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ORAL ANTICOAGULANTS AS STROKE PREVENTION IN THE SETTING OF ATRIAL FIBRILLATION AND CANCER

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background

Cancer patients have elevated risk of both stroke and bleeding in comparison to individuals without cancer. The general population is ageing and the group of patients with atrial fibrillation (AF) and cancer concomitantly becomes larger; however, there is lack of stroke prevention guidelines addressing these patients. The aim of this thesis was to describe stroke prevention with oral anticoagulants (OACs) in AF patients with cancer and to estimate net benefit.

Methods and Results

Register data on all patients with at least one registered diagnosis of AF in the Swedish Patient Register between 1 July 2005 and 31 December 2017 were cross-matched with the Drug Register, the Cancer Register, the Cause of Death Register, and the Riksstroke Register. Patients with a new cancer diagnosis within the past year and patients without a cancer diagnosis in the last five years were included.

Study I: Propensity score matching for the likelihood of being on OAC treatment after having been diagnosed with AF was used to study patients with and without OAC treatment. Cancer (n=14,472) and non-cancer (n=304,286) patients were analysed separately. Amongst cancer patients, there was an overall net benefit of OAC use for the composite outcome of ischaemic stroke, extracranial arterial thromboembolism, bleedings, and death (hazard ratio [HR]: 0.81, 95% confidence interval [CI]: 0.78–0.85). This result is driven by patients with at least intermediately increased stroke risk. Limiting follow-up to one year and accounting for the competing risk of death, there was a net cerebrovascular benefit for OACs generally (subhazard ratio [sHR]: 0.67, CI: 0.55–0.83) and for non-vitamin K antagonist OACs (NOACs) (sHR: 0.65, CI: 0.48–0.88) over warfarin.

Study II: In Riksstroke we identified all AF patients who had suffered an ischaemic stroke. Amongst cancer patients (n=1,518) the proportion prescribed OACs at discharge increased by 40.2% after NOACs were introduced, compared with 69.3% in non-cancer patients (n=50,953), even though stroke and bleeding risk scores remained similar between the patient groups. OAC dispensation during the following year increased less in cancer patients (43.8% to 64.5%) than in non-cancer patients (46.0% to 74.9%), and the median time to OAC dispensation was significantly longer (94 vs. 30 days) after the introduction of NOACs.

Study III: There was no difference in net cerebrovascular benefit amongst patients with cancer (n=8,228) and without cancer (n=323,394) during the year following OAC initiation adjacent to AF diagnosis accounting for the competing risk of death (sHR: 1.12, CI: 0.98–

1.29). Cancer patients had a higher risk of non-fatal bleedings (sHR: 1.69, CI: 1.56–1.82). NOACs were associated with lower risk of both cerebrovascular events and bleedings compared to warfarin. Amongst NOAC treated, cancer was not a predictor of intracranial bleedings.

Conclusions

AF patients with cancer have a net benefit from OAC treatment and may be treated according to current AF guidelines for the general AF population, but they should be monitored closely for bleedings. NOACs appear safer than warfarin, but seem underutilised as secondary prevention after ischaemic stroke amongst cancer patients.

LIST OF SCIENTIFIC PAPERS

I. **Atterman A**, Friberg L, Asplund K, Engdahl J.
Net benefit of oral anticoagulants in patients with atrial fibrillation and active cancer: a nationwide cohort study.
Europace 2020;22:58-65.

II. **Atterman A**, Asplund K, Friberg L, Engdahl J.
Use of oral anticoagulants after ischaemic stroke in patients with atrial fibrillation and cancer.
Journal of Internal Medicine 2020: doi: 10.1111/joim.13092.

III. **Atterman A**, Friberg L, Asplund K, Engdahl J.
Atrial fibrillation, oral anticoagulants, and concomitant active cancer: benefits and risks.
Submitted.

CONTENT

LIST OF ABBREVIATIONS

AF	Atrial fibrillation
ASCOD	Atherosclerosis, Small-vessel disease, Cardiac pathology, Other causes, or Dissection
ATC	Anatomic Therapeutic Chemical classification system
CCS	Causative Classification of Stroke
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CrCl	Creatinine clearance calculated by the Cockcroft-Gault formula
CYP	Cytochrome P450
HR	Hazard ratio
ICD-10	International Classification of Disease-10th Revision
INR	International normalised ratio
LMWH	Low molecular weight heparin
NOAC	Non-vitamin K antagonist oral anticoagulant
OAC	Oral anticoagulant
OR	Odds ratio
PCI	Percutaneous coronary intervention
PT	Prothrombin time
sHR	Subhazard ratio
TIA	Transient ischaemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
TTR	Time in therapeutic range
VKA	Vitamin K antagonist

1 INTRODUCTION

As clinical evidence of the stroke preventive effect of oral anticoagulants (OACs) amongst individuals with atrial fibrillation (AF) has increased, and the cardio-oncological perspective has attracted more attention (not least by the foundation of the European Society of Cardiology Council of Cardio-Oncology in 2018), interest has been directed towards OAC use amongst patients with AF and concomitant cancer. Contrary to other complicating comorbidities such as dialysis-dependent kidney disease or previous major bleedings, nothing is mentioned about how to handle OAC as stroke prevention in the presence of cancer in the current European AF guidelines.[1] The same applies to the American[2] and Australian AF guidelines,[3] which implies that treatment decisions regarding this group of patients has been very much left to the individual clinician.

Current statistics show an ageing population and ever more cancer survivors. This is to a large extent an effect of modern treatments turning cancer into more of a chronic and manageable disease. As OAC treatment has become established through accumulated scientific evidence and updated AF guidelines in the general population, there is an increasing need for guidelines on stroke prevention in the growing population of AF patients with cancer.

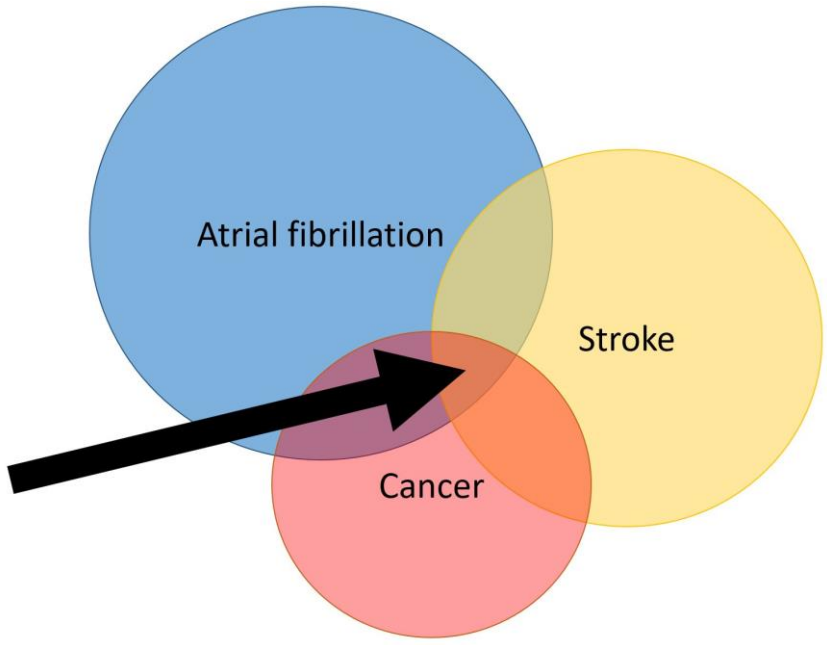

Figure 1: Illustration of the comorbidity intersect between AF, ischaemic stroke, and cancer.

2 BACKGROUND

2.1 ATRIAL FIBRILLATION

The electrocardiographic definition of AF is the presence of irregular R-R intervals without P waves, and an atrial rate of > 300 per minute for a minimum of 30 seconds. AF is considered to be paroxysmal if the attacks terminate within seven days, and persistent if the attacks last longer than seven days. Permanent AF is defined as an accepted AF where no rhythm control is pursued. The major risk factors for the development of AF – except ageing and genetic predisposition – are hypertension, coronary artery disease, obesity, heart failure, and diabetes.[1]

AF has an overall prevalence of at least three per cent in the adult population,[4,5] making it the most common chronic arrhythmia in patients over 65 years. AF is frequently clinically silent and therefore undiagnosed, as shown in screening studies.[6] It has been estimated that up to one third of all AF is yet undiagnosed.[1] As prevalence increases with age, it has been estimated to be about 14–24% in 80 to 85-year-olds.[7,8] The prevalence of AF has doubled in the last decade and by the year 2060 it is expected to double once more amongst people over the age of 55 years in Europe.[8,9]

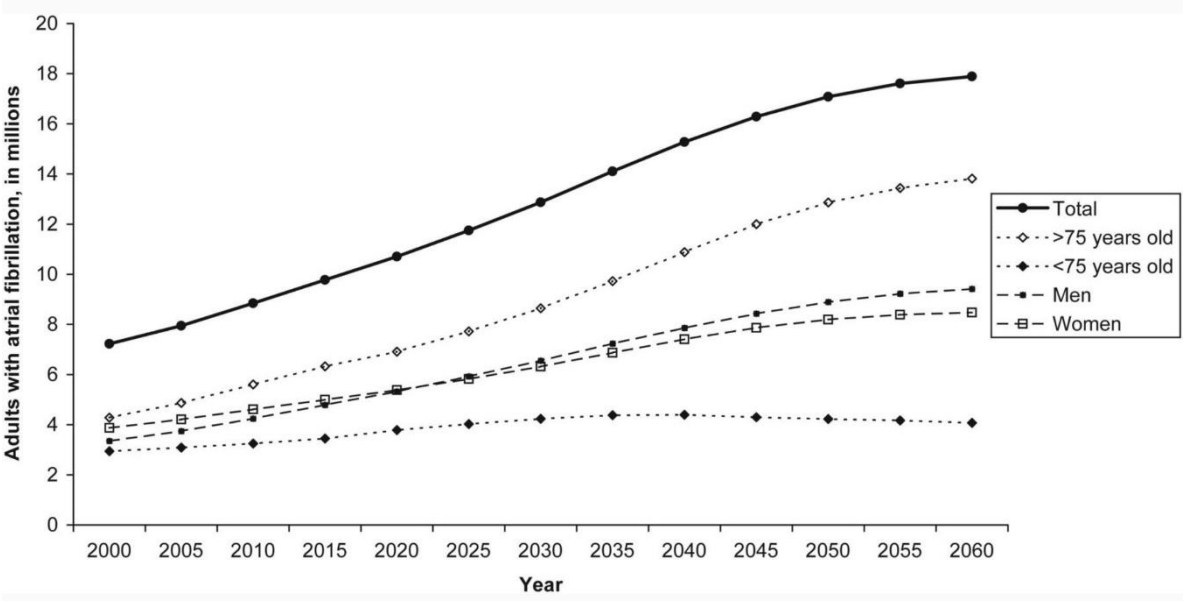

Figure 2: Projected number of adults with AF in the European Union between 2000 and 2060. Graph reproduced with permission from the publisher.[8]

AF is associated with a 1.5-fold mortality amongst men and a doubled mortality amongst women,[10-12] as well as with increased morbidity such as heart failure and stroke.[11,13,14]

2.2 CARDIOEMBOLIC STROKE

Ischaemic stroke, defined as an acute focal neurological symptom for more than 24 hours or with radiological evidence of an acute lesion in a corresponding neuroanatomical location, is most often caused by occlusion of a cerebral artery. In cardioembolic stroke, the occlusion is caused by an embolus emanating from a thrombus formed in the heart due to disturbed blood flow.

There are several stroke classification systems, of which Trial of Org 10172 in Acute Stroke Treatment (TOAST) belongs to the most used and well-known in clinical practice. It identifies the following stroke etiologies: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-artery occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology. For the diagnosis of cardioembolic stroke, at least one cardiac source for an embolus must be identified.[15] The stroke classification systems Causative Classification of Stroke (CCS)[16] and Atherosclerosis, Small-vessel disease, Cardiac pathology, Other causes, or Dissection (ASCOD)[17] acknowledge the coexistence of multiple stroke risk factors, thereby assigning a certain probability to all identified stroke mechanisms. TOAST, CCS, and ASCOD to a large extent agree on the high-risk sources of cardiac embolism, amongst which one of the most important is AF.

Table 1

High-risk sources of cardiac embolism according to the stroke classification systems TOAST, CCS, and ASCOD.[18]
Mechanical prosthetic heart valve
Atrial fibrillation/flutter
Left atrial/ventricular thrombus
Myocardial infarction within one month
Dilated cardiomyopathy
Infective endocarditis
Regional akinesis of left ventricle
Atrial myxoma
Mitral stenosis
Patent foramen ovale

Non-valvular AF, regardless if intermittent or whether it is secondary to another disease or procedure, is associated with an approximately five-fold higher risk of ischaemic stroke and is the leading cause of cardioembolic stroke.[11,13,19,20] Cardioembolic strokes constitute about one-third of all ischaemic strokes, are more prevalent with increasing age, cause more severe sequels, and have the highest recurrence rates and lowest survival rates.[4,21-23]

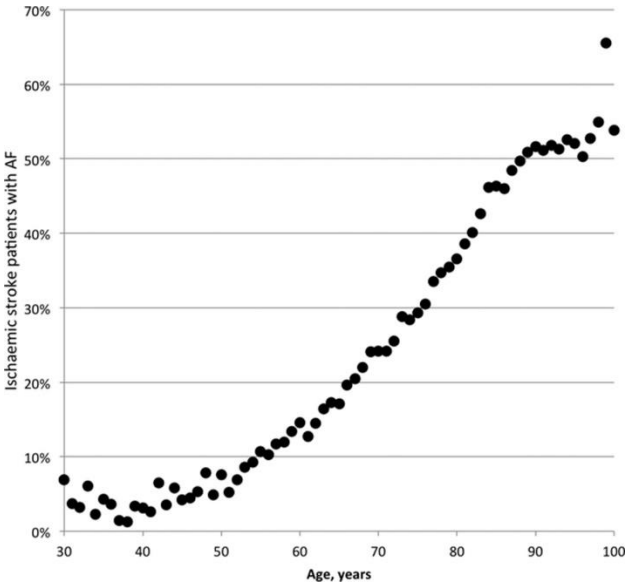

Figure 3: Prevalence of AF in relation to age in patients with ischaemic stroke. Graph reproduced with permission from the publisher.[21]

The importance of cardioembolic stroke due to AF is illustrated by the fact that although the overall stroke incidence has decreased partly thanks to better treatment of atherosclerotic risk factors, cardioembolic strokes have increased nearly three-fold amongst patients over 80 years in the last 25 years. Based on estimations, they may triple again by 2050.[24,25]

Previous studies have shown that embolic stroke of undetermined source is often associated with subclinical AF, and that prolonged heart-rhythm monitoring increases chances of detecting AF.[26,27] The hypothesis that many cryptogenic strokes are in fact cardioembolic is supported by a recent study using radiological characterisation of thrombi.[28] This hints a risk of underestimating AF related strokes due to AF often being asymptomatic[29].

2.3 STROKE PREVENTION WITH ORAL ANTICOAGULANTS

Even though the century old hypothesis about AF causing cardioembolic stroke has been modified by other contributing mechanisms,[30] scientific evidence has been accumulated over time that treatment with OACs reduces the risk of ischaemic stroke by about 70% in patients with AF.[31-33] However, stroke risk varies widely depending on the individual patient's other stroke risk factors.[13] This explains why prediction of ischaemic stroke in AF patients in order to identify patients at higher risk who would therefore benefit the most from OAC therapy, has been highlighted in AF guidelines.

Estimating stroke and bleeding risk

Several predictive models have been developed to help guide the clinical decision of starting OAC therapy in AF patients. The CHA_2DS_2-VASc stroke risk score, which is an extension of

the previous $CHADS_2$ score, was presented by Lip et al. in 2010, giving one point for each of congestive heart failure, hypertension, diabetes, vascular disease, female sex, age 65–74 years and two points for each of prior stroke and age ≥ 75 years. The score was created in a cohort of 1,084 adult patients with non-valvular AF off warfarin treatment at baseline and whose thromboembolic status after one year of follow-up was known. The outcome was the composite of thromboembolic events, defined as either ischaemic stroke, peripheral embolism, or pulmonary embolism. The conclusion of the original article was that the score has good ability in identifying patients with truly low stroke risk, thus not in the need of OAC.[34] According to analyses of the CHA_2DS_2-VASc stroke risk score in Swedish hospital data, stroke risk ranges from 0.2% per year amongst individual with zero points, to 14.0% per year for those with nine points.[35] The CHA_2DS_2-VASc stroke risk score has been externally validated many times[36] and is now recommended by both the European and the 2019 update of the American AF guidelines. These guidelines recommend NOACs with warfarin as an alternative at a CHA_2DS_2-VASc score of one or higher, not counting points for female sex.[1,2]

Several bleeding prediction scores have been created in order to help identify the patients at highest risk of bleeding, for example the HAS-BLED score[37]. Compared with the $HEMORR_2HAGES$[38] and the ATRIA bleeding risk[39] scores, HAS-BLED has shown better discrimination. However, all scoring systems only have modest performance and low predictive properties.[40,41] In line with the European AF guidelines, the European Society of Cardiology Working group on Cardiovascular Pharmacotherapy and the European Society of Cardiology Council on Stroke conclude that OAC treatment is recommended at increased stroke risk according to the CHA_2DS_2-VASc risk score and after assessment of the HAS-BLED bleeding risk score in order to find manageable bleeding risks.[1,42]

Net benefit of oral anticoagulants

It is recommended that stroke prevention with OAC amongst AF patients be preceded by an estimation of the individual net benefit, meaning that benefit from the reduction in ischaemic stroke risk must exceed the harm from increased bleeding risk with OAC therapy. A large meta-analysis of antithrombotic treatment in AF patients concluded that the increased bleeding risk was lower than the stroke reduction, thus indicating net benefit of warfarin over both platelet inhibition and no antithrombotic treatment.[31] This conclusion was confirmed by Friberg et al. in an observational register based study of nationwide Swedish AF data.[43] Corresponding results were later seen for the NOAC apixaban.[44] The European AF guidelines recommend OAC in all patients with AF, except for patients with very low stroke risk,[1] thus aligning with the concept of net benefit. Studies have shown that even in older patients with frequent falls, or with cognitive impairment, the stroke risk of untreated AF patients is estimated to exceed the bleeding risk with OAC.[45,46] There are several examples of the net benefit of OACs amongst the elderly: In a prospective randomised open-label trial of warfarin versus aspirin amongst AF patients over 75 years of age, a net benefit defined as reduction of fatal or disabling ischaemic or haemorrhagic stroke or other arterial embolism was seen for warfarin over aspirin.[47] Also an observational study of very elderly patients (aged ≥ 85 years) with AF showed a net benefit of OACs since the reduction of thromboembolic events outweighed the hemorrhagic risk.[48]

Vitamin K antagonist oral anticoagulants

Warfarin, which is the only registered vitamin K antagonist (VKA) oral anticoagulant in Sweden, inhibits vitamin K oxide reductase and thereby the carboxylation of the vitamin K dependent coagulations factors II, VII, IV and X.

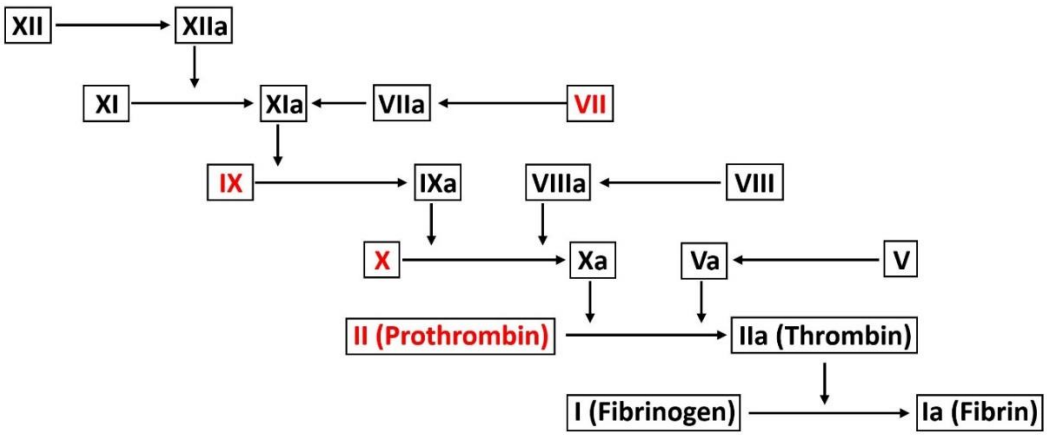

Figure 4: Vitamin K-dependent coagulation factors (red) in the coagulation cascade.

It is metabolised mainly by cytochrome P450 (CYP) 2C9 and is therefore not dependant on kidney function.[49] The anticoagulation effect needs to be continuously monitored through blood measurements of the prothrombin time and international normalised ratio (PT-INR), with a preferable value between 2.0 and 3.0 and a time in therapeutic range (TTR) ideally over 70%, which is achieved in Sweden according to validations.[50]

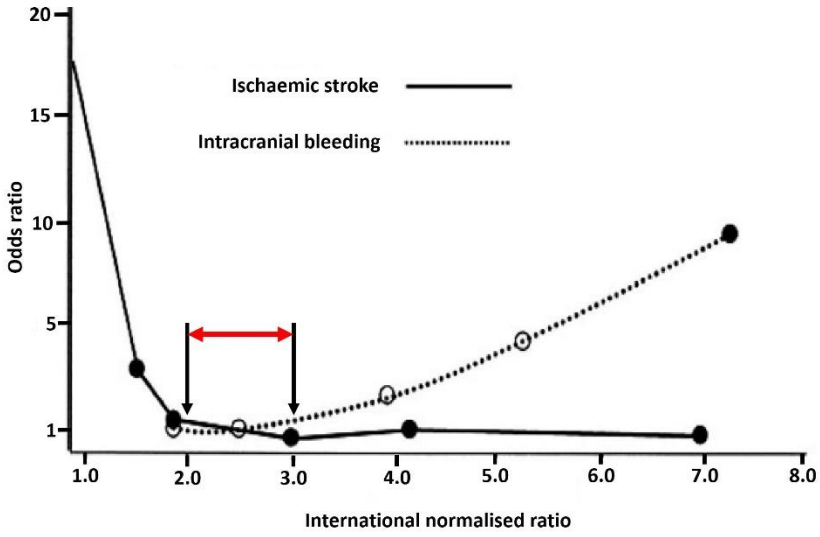

Figure 5: Odds ratios for ischaemic stroke and intracranial bleeding related to INR. Red arrow marks PT-INR 2.0–3.0. Modified from Fuster et al. 2006.[51]

Food and drug interactions are common and bridging with low molecular weight heparin (LMWH) is often used to overcome periods of low anticoagulation. The antidote three- or four-factor prothrombin complex concentrate acts instantly, while vitamin K takes up to four to six hours to reach full effect.[52]

Non-vitamin K antagonist oral anticoagulants

In December 2011 dabigatran was the first non-vitamin K antagonist oral anticoagulant (NOAC) subsidised for stroke prevention in patients with AF in Sweden. It was later followed by rivaroxaban in October 2012, apixaban in May 2013, and edoxaban in June 2016. Dabigatran is a direct thrombin inhibitor, whereas apixaban, rivaroxaban and edoxaban are direct factor Xa inhibitors.[53]

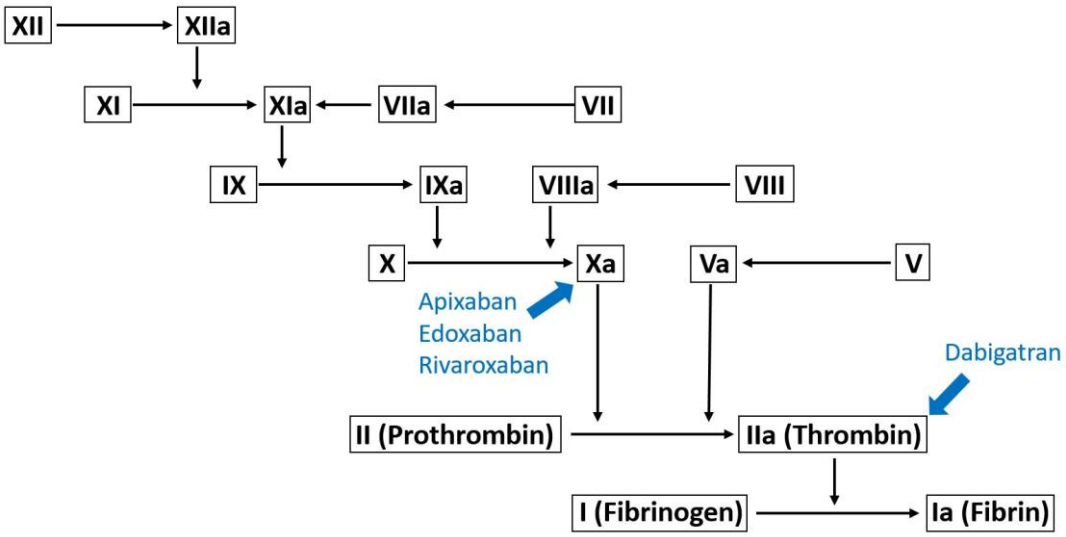

Figure 6: Targets of non-vitamin K antagonist oral anticoagulants in the coagulation cascade. Modified from Hoffman et al. 2017.[54]

Since their introduction NOAC prescriptions have increased amongst AF patients, surpassing warfarin overall.[55] Compared with warfarin, NOACs have less food interaction, a wider therapeutic window, and no need for the continuous monitoring of the anticoagulation effect. However, impaired kidney function, low body weight, and higher age are factors that should be taken into consideration.[1] NOACs interact with glycoprotein-P and are metabolised by CYP 3A4, which could interfere with other drugs, including chemotherapy. Idarucizumab and andexanet alfa are the antidotes approved in Sweden for dabigatran and apixaban/edoxaban/rivaroxaban, respectively.

VKA vs. NOAC

VKA and NOACs have been compared in several clinical drug trials, amongst which the most important are summarised in Table 2. NOACs have been shown to be at least as effective with less intracranial bleedings but a higher risk of gastrointestinal bleeding compared with warfarin at high mean TTR[32,56,57] In the presence of mitral stenosis or mechanical prosthetic heart valve, however, VKA is considered the only safe anticoagulant.[58]

Table 2

Currently available NOACs in Sweden							
Drug	**Target**	**Half-life (hours)**	**Dosing frequency (daily)**	**Renal dosing adjustments**	**Drug interactions**	**Reversal agent**	**Major trial comparing drug to warfarin**
Dabigatran	Thrombin	12–17	Twice	CrCl<30 mL/min: contraindicated	Proton pump inhibitors, antacids, dronedarone, P-gp-inhibitors	Idarucizumab	RE-LY[59]
Rivaroxaban	Factor Xa	5–13	Once	CrCl<30 mL/min: avoid use	CYP3A4 inhibitors, P-gp-inhibitors	Andexanet alfa	ROCKET-AF[60]
Apixaban	Factor Xa	9–14	Twice	CrCl<25 mL/min: limited data	CYP3A4 inhibitors, P-gp-inhibitors	Andexanet alfa	ARISTOTLE[61]
Edoxaban	Factor Xa	10–14	Once	CrCl 15–50 mL/min: dose reduction, CrCl<15 mL/min: not recommended	CYP3A4 inhibitors, P-gp-inhibitors	Andexanet alfa	ENGAGE AF-TIMI 48[62]

Undertreatment

Although the stroke preventive effect of OACs in AF patients is superior to treatment with platelet inhibitors or no antithrombotic treatment,[44,63] several studies have indicated problems with OAC undertreatment in the general AF population.[64-67] Also, having a cancer diagnosis has been shown to increase the odds of not receiving anticoagulation therapy.[68]

After the 2012 update of the European AF guidelines and the introduction of NOACs, temporal changes have been seen. In the Stockholm region, for example, the use of OACs

amongst AF patients with moderate or high stroke risk increased from 54% to 82% between 2011 and 2018.[69] Reports from the nationwide Swedish stroke register, Riksstroke, regarding patients suffering an ischaemic stroke, shows an increase in secondary prevention in AF patients from 30% in 2005 to 80% in 2019.[70,71]

2.4 CANCER

Cancer comprises a large group of diseases characterised by uncontrolled growth and division of cells, and the ability to metastasise. With age, as exposure to various risk factors accumulate and cellular repair mechanisms become less effective, cancer risk increases.[72]

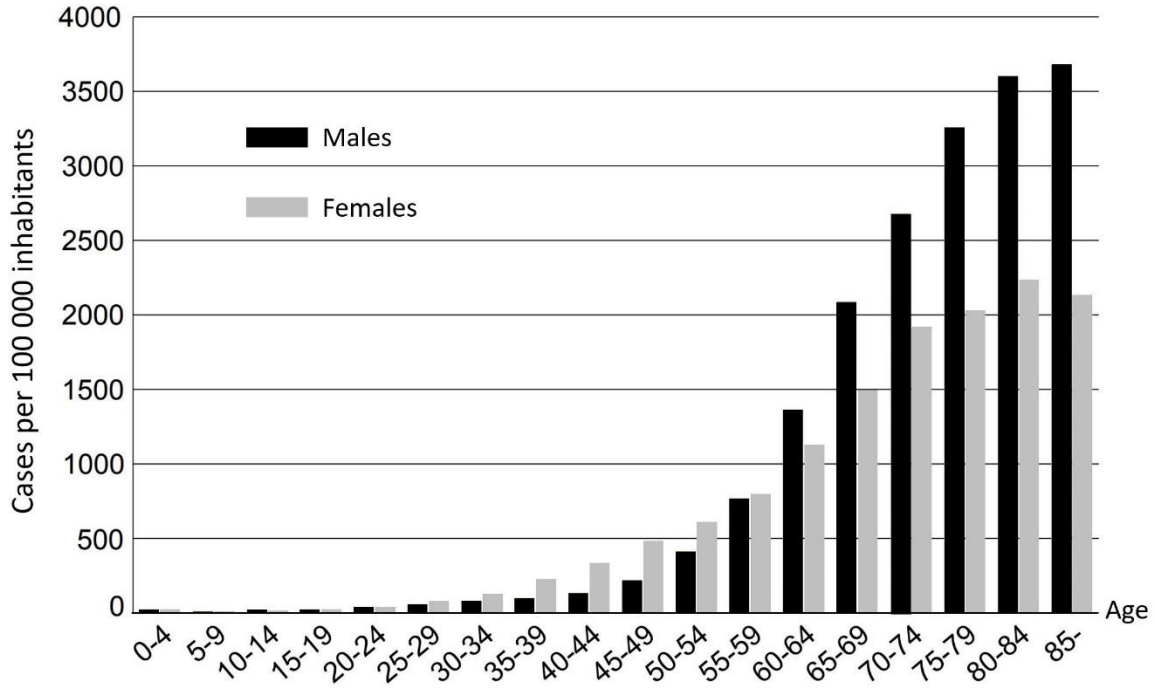

Figure 7: Cancer incidence in Sweden 2014–2016.[73]

Cancer is the second most common cause of death in Europe after cardiovascular disease. Europe-wide, there has been a 50% increase in cancer incidence in the last two decades, mainly due to an ageing population, life style factors and earlier diagnosis. However, during the same time period, cancer mortality increased by only 20% due to increased survival, which amongst other reasons, is probably an effect of improved therapy strategies. The age-adjusted cancer survival rates in Sweden between 1980 and 2015 are illustrated in Figure 8. Accounting for an ageing population, age-adjusted cancer mortality is decreasing.[73,74]

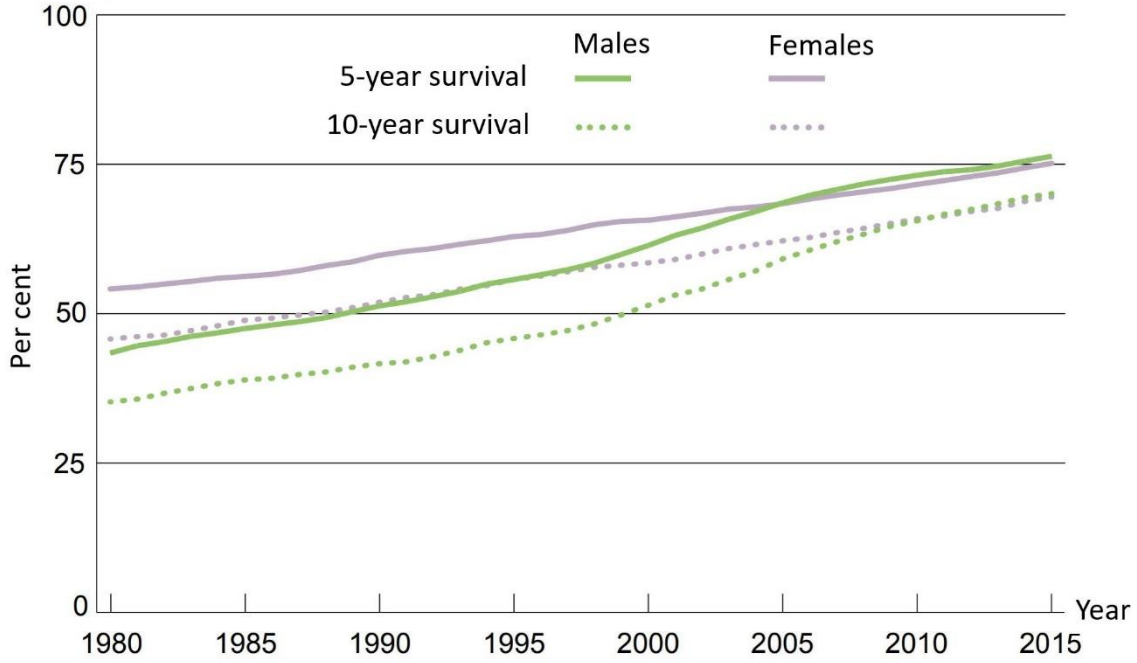

Figure 8: Age-standardised cancer survival in Sweden 1980-2015.[73]

2.4.1 Related conditions

Several conditions are associated with cancer, either directly or due to diagnostic or therapeutic procedures. Cancer overall is associated with increased mortality, but rates differ between cancer types and stages, ranging from patients surviving cancer without relapses, to those diagnosed with an already advanced disease followed by death within a short time period. For several cancer types, mortality rates overlap with those of several cardiovascular conditions. A recent register-based study covering nearly one third of the population in the USA in the last four decades showed that cancer patients have on average a two- to six-times higher mortality due to cardiovascular disease compared to the general population. Amongst cancer patients, 38% died from cancer and 11% from cardiovascular disease. In cancer survivors diagnosed with cancer before age 55, a more than ten-times higher risk of cardiovascular death was seen than in the general population.[75]

Atrial fibrillation

Several previous studies have observed correlations between cancer and AF,[76-79] and some have indicated higher cancer incidence after an AF diagnosis.[80-82] Chances to be diagnosed with AF may be greater for patients with frequent hospital visits due to cancer and even though there is methodological heterogeneity amongst studies of AF prevalence in cancer patients, various mechanisms explaining this association have been presented: inflammatory effects on the atria,[83,84] up-regulation of the sympathetic nervous system,[85] and cancer

associated venous thromboembolism including pulmonary embolism[86] inducing right heart strain causing tachycardia, including AF. There are several reasons other than stress and surgery for AF to exist amongst cancer patients, for example anti-tumoural drugs, tyrosine kinase inhibitors, immunotherapy, and radiotherapy, which have the capacity to cause direct AF inducing cardiotoxicity.[87,88]

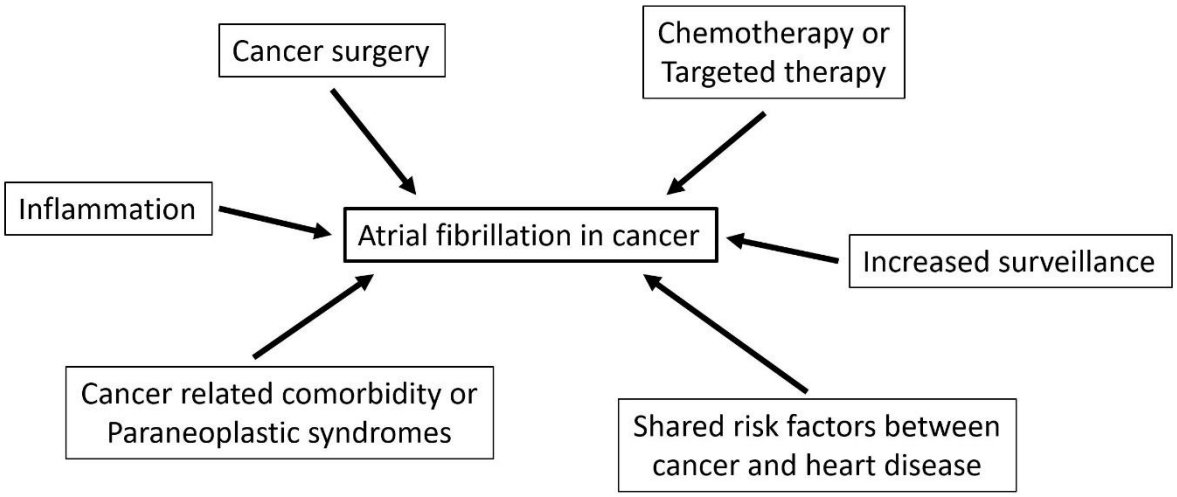

Figure 9: Possible causes for AF diagnosis in cancer patients. Modified from Guha et al. 2019.[89]

Besides a higher observed prevalence of AF in cancer populations, AF has been associated with twice as high risk for thromboembolism, six times higher risk for heart failure,[90] and over six times higher mortality after lung cancer surgery.[91] This could also be partly an effect of more aggressive and potentially more AF-inducing cancer treatment in individuals with advanced disease[92].

Stroke

Compared with the general population, cancer patients have an approximately doubled stroke risk,[93-95] longer hospital stays and a generally worse prognosis including neurological impairment after a stroke.[96-98] Cryptogenic stroke is about twice as common in patients with cancer, with an estimated proportion of 40–50%,[23,99-104] which suggests the existence of cancer specific stroke mechanisms. It has been hypothesised that cancer induces a hypercoagulable state[94,101,105] through multiple mechanisms. The most important among these include endothelial damage due to inflammation, and platelet and coagulation system activation. Several mechanisms associate chemotherapy to ischaemic stroke, by which endothelial injury, vasculitis, vasospasm, venous stasis, or general activation of the

coagulation cascade is induced. Radiotherapy of the head and neck region is associated with increased stroke risk despite no clear dose-response relationship between radiotherapy and carotid stenosis. Other less common cancer associated causes of ischaemic stroke are tumour and metastasis embolisation and direct compression of cerebral vessels.[99]

Table 3: Cancer specific mechanisms of cerebral infarction. Modified from Neilson et al. 2018.[106]

Mechanism	**Pathophysiology**	**Association**
Hypercoagulability	Activation of selectin and tissue factor, cytokine release	Adenocarcinoma of breast, lung, gastrointestinal tract
Non-bacterial thrombotic endocarditis	Non-inflammatory platelet-fibrin vegetations on structurally normal valves in the absence of bacteremia	Adenocarcinoma of breast, lung, gastrointestinal tract
Radiation vasculopathy	Accelerated atherosclerosis in carotid arteries, Moyamoya in the brain	Head and neck tumours, acute lymphatic leukaemia
Tumour embolism	Direct embolisation of tumour, malignant cells	Atrial myxoma, sarcoma, metastatic tumours to heart
Paradoxical embolism	Patent foramen ovale, right-to-left shunt	All
Chemotherapy-induced	Endothelial injury, venous stasis, vasculitis, vasospasm, widespread activation of the coagulation cascade	Cisplatin, methotrexate, L-asparaginase, tamoxifen, bevacizumab
Local tumour compression	Stasis, thrombosis, spasm of cerebral vasculature	Tumours metastatic to the dura, meningioma, pituitary adenoma

The association between cancer and stroke is correlated to several aspects of cancer, ranging from stroke levels of the general population to very increased stroke risk. Analogous to venous thromboembolism[107] certain cancer types have shown stronger association with ischaemic stroke than others. Some of the most common cancers, like prostate and breast cancers have been associated with similar or just a slightly increased stroke risk whereas patients with metastasised and newly diagnosed cancer have an increased stroke risk, compared to those without cancer.[94,95,108] Particularly adenocarcinoma of the lung, pancreas, ovary, and colon have been linked to ischaemic stroke.[93,95,99,109-111] In a large nationwide Swedish register based cohort study of all 820,491 patients with a cancer diagnosis between 1987 and 2008, the overall risk – expressed as standardised incidence ratio – of ischaemic

stroke during the first six months after any type of cancer diagnosis was 1.6. This risk more than doubled for cancer of the lungs, pancreas, small intestine, endocrine glands, nervous system, and leukaemia compared with the non-cancer population.[108]

Beyond various cancer specific stroke mechanisms, the classical stroke risk factors like hypertension, diabetes, smoking, carotid artery stenosis, and AF are considered the altogether most important ones, also amongst patients with cancer.[99] There are some studies suggesting no increased risk of cardioembolic stroke amongst cancer patients.[94,112] On the other hand, an imaging study of ischaemic stroke in patients with active cancer showed that around 67% of the strokes appeared as multiple embolic events, consistent with clot formation and embolisation,[113] which anatomically shares the radiological pattern of cardioembolic stroke due to AF. These findings raise questions of possible underestimation of AF occurrence and importance.

Studies suggesting a higher risk for ischaemic stroke amongst AF patients with cancer than without cancer have used imprecise definitions of active cancer, strict subgrouping, or have studied relatively small populations.[114,115] Despite a possibly cancer-induced hypercoagulable state, several observational studies suggest that the attributable stroke risk from cancer is low compared with AF, indicating AF as the overall most important stroke risk factor.[116-119]

Bleeding

Several bleeding risk factors have been found in cancer patients. Even though studies differ with varying definitions and methods, some common factors have been identified: higher age, prior bleedings, anaemia, thrombocytopenia, treatment with platelet inhibitors, kidney failure, surgical procedures, general frailty, and cancers involving mucous membranes and metastases.[120-123] Compared with the general population, cancer patients on OAC have approximately six-times higher bleeding risk,[124-126] where labile TTR contributes[127-130]. Additionally, there are potential interactions between OACs and anti-tumoural treatment, as mentioned above (chapter 2.3).

2.4.2 Atrial fibrillation and stroke prevention

It can be clinically challenging to prescribe OAC to cancer patients because they have an increased risk of both ischaemic stroke and bleeding, including haemorrhagic stroke. These are associated with higher mortality, greater functional impairment, lower quality of life, and higher health and social care costs.[131-133]

Stroke risk scores

There have been very few validations of the recommended and established stroke risk scores in cancer cohorts, and the issue of the predictive ability has been discussed. A Taiwanese validation amongst cancer patients showed that an increasing $CHADS_2$ stroke risk score was

significantly correlated with risk of thromboembolism (stroke, peripheral emboli, or pulmonary emboli) in patients with AF at baseline, but not in patients with new-onset AF.[90] Another validation in a cancer cohort showed that $CHADS_2$ has a better predictive ability for stroke than CHA_2DS_2-VASc for baseline AF.[134] Yet another validation in hospitalised patients in Denmark with a recent cancer diagnosis showed that cancer changes the predictive abilities of CHA_2DS_2-VASc stroke risk score, implying cautious use.[114]

Low molecular heparin

In the growing field of cardio-oncology, the question of AF and stroke prevention in the presence of cancer has raised a growing interest in the last few years. LMWH in non-therapeutic dosage seems to be the clinician's choice in about one third of AF patients with cancer according to a recent Italian single-centre study.[68] A possible reason for choosing LMWH is that available safety data on OAC treatment in cancer patients originates from randomised controlled trials studying treatment of venous thromboembolism, compared with LMWH.[135-139] Although clinicians might regard LMWH a safer alternative to OAC in cancer patients, bridging use of LMWH in these patients has been associated with increased bleeding without decreasing thrombotic risk.[140] In the setting of cancer-associated venous thromboembolism, a meta-analysis of OACs versus LMWH shows that LMWH has better efficacy than VKA, but not better safety, and that LMWH and NOACs appear equal regarding both efficacy and safety.[141] However, there is no evidence for stroke prevention with LMWH in AF patients,[142] and it has been recommended that LMWH should be avoided in the acute phase after an ischaemic stroke in AF patients due to increased bleeding risk.[143]

3 AIMS

The overall aim of this thesis was to increase knowledge about stroke prevention with OACs in the setting of AF and concomitant cancer regarding use and patient outcomes.

The specific aims were:

To assess net benefit of OAC treatment in patients with AF and cancer.
To describe secondary prevention with OACs after ischaemic stroke amongst AF patients in the presence of concomitant cancer, before and after the introduction of NOACs.
To study the influence of cancer on the benefit-risk relationship in AF patients with OAC treatment.

4 MATERIAL AND METHODS

4.1 OVERVIEW OF THE STUDIES INCLUDED IN THE THESIS

Study	Study I	Study II	Study III
Aim	To estimate net cerebrovascular benefit of OAC treatment in patients with AF and cancer.	To study secondary prevention with OACs after ischaemic stroke amongst AF patients in the presence of cancer, before and after the introduction of NOACs.	To determine the influence of cancer on the benefit-risk relationship in OAC treated AF patients.
Hypothesis	Cancer patients with AF benefit from OAC treatment.	OAC as secondary prevention after ischaemic stroke has increased after NOAC introduction, regardless of cancer status.	Cancer does not compromise cerebrovascular benefit of OAC treatment.
Design	Cohort study	Cross-sectional and cohort study	Cohort study
Data sources	Patient Register, Cancer Register, Cause of Death Register, Drug Register	Riksstroke, Patient Register, Cancer Register, Cause of Death Register, Drug Register	Patient Register, Cancer Register, Cause of Death Register, Drug Register
Study population	All AF patients in Sweden	All post-ischaemic stroke patients with AF in Sweden	All OAC treated AF patients in Sweden
Number of study participants	Before/after propensity score matching: 22,596/14,472 (cancer), 440,848/304,286 (non-cancer).	1,518 (cancer), 50,953 (non-cancer).	8,228 (cancer), 323,394 (non-cancer).
Exposure	OAC	Cancer, NOAC introduction	Cancer
Comparison	Treatment vs. no treatment	Cancer vs. non-cancer, 2005–2011 vs. 2012–2017	Cancer vs. non-cancer
Outcomes	1) Cerebrovascular benefit 2) Composite of adverse events 3) Bleedings 4) Death	1) OAC prescription at discharge 2) OAC dispensation after discharge	1) Cerebrovascular benefit 2) Bleedings
Time of data collection	1 July 2005 to 31 December 2017.	1 July 2005 to 31 December 2017.	1 July 2005 to 31 December 2017.
Statistics	Propensity score matching, survival analysis (Cox regression), competing risk analysis	Descriptive statistics, survival analysis (Cox regression), cluster analysis, competing risk analysis	Survival analysis (Cox regression), competing risk analysis
Main findings	1) AF patients with cancer had a net cerebrovascular benefit the year following cancer diagnosis when treated with OACs. 2) AF patients with cancer, and at least intermediate stroke risk, had a lower risk of adverse events including death when treated with OACs.	1) AF patients with cancer were less likely to receive OAC treatment after ischaemic stroke. 2) Secondary prevention has increased since NOAC introduction, but less and with delay amongst cancer patients.	Amongst OAC treated AF patients: 1) Net cerebrovascular benefit was similar for patients with and without cancer. 2) Cancer was associated with an overall increased risk of non-fatal bleedings.
Publication	*Europace* 2020.	*J Intern Med* 2020.	*Submitted*.

4.2 REGISTERS

This thesis is based on register data of all patients with an AF diagnosis in the Swedish national Patient Register during the time period 1 July 2005 and 31 December 2017. Using the twelve-digit personal civic registration number, which is given to every permanent resident in Sweden upon birth or immigration for life-long use, cross-linking to other health registers was coordinated by the National Board of Health and Welfare. The dataset was anonymised according to regulations before being handed over to us for research purposes. The national Patient Register[144] collects data on all admissions and visits at public hospitals and hospital-associated outpatient units in Sweden since 1987. Since 1 July 2005 all dispensations of prescribed medication in Sweden are registered in the Drug Register,[145] allowing cross-matching with other Swedish health registers. The Swedish Cause of Death Register is highly complete; all deaths reported to the tax authority since 1997 are included.[146] The Cancer Register is prospective and collects information on diagnosed malignancies.[147] Riksstroke,[148] which is a prospective register established in 1994, collects information on comorbidity, therapeutic procedures, pharmacological treatment, and social needs and efforts in conjunction with stroke events. It was created to help develop and improve stroke care in Sweden at any of the 72 hospitals throughout Sweden that admit acute stroke cases.

4.3 STUDY DESIGN AND STUDY POPULATION

4.3.1 Definitions

General inclusion and exclusion criteria

All studies of this thesis were restricted to patients with AF, with either active cancer (cancer patients) or no cancer (non-cancer patients). Active cancer was defined by a new cancer diagnosis registered in the Patient Register and/or the Cancer Register within one year before baseline, not preceded by any cancer diagnosis up to five years before baseline. Individuals were, on the other hand, regarded as non-cancer patients if they had not received any cancer diagnosis during the five years before baseline. Basalioma was excluded from the cancer definition because it does not share the metastatic feature of other cancers. Patients under 18 or over 100 years of age were excluded, as well as patients with an absolute cardiological indication for OACs (mitral stenosis, mechanical heart valve), or who died before start of follow-up.

Comorbidity

In Studies I and III, comorbidity at baseline was defined by diagnosis codes registered in the Patient Register back to 1997 when the International Classification of Disease-10th Revision (ICD-10) was implemented in Swedish health care. In Study II, additional information was

collected from the Riksstroke register regarding hypertension and diabetes diagnoses, as well as for social factors such as need for home assistance. Because the impact of alcohol use is difficult to measure but is still a potential confounder when studying use of OACs, we created a variable named alcohol-related disease. This is based on the alcohol index used by the Public Health Agency of Sweden and consists of diagnosis codes from the Cause of Death register used by the National Board of Health and Welfare to describe alcohol-related death.[149]

Anticoagulants

For the main analyses we studied OACs that are defined as either VKA (warfarin) or NOACs. Use was defined as at least one dispensed prescription. In Study II we additionally studied OAC prescription at discharge after ischaemic stroke according to the Riksstroke register.

Risk scores

The CHA_2DS_2-VASc stroke risk score[34] was defined as one point each for heart failure, hypertension, diabetes, vascular disease, female sex, age 65–74 years and two points each for prior stroke and age ≥ 75 years. In accordance with previous studies and current AF guidelines,[1,150] the score did not include points for female sex. A CHA_2DS_2-VASc score of zero was regarded as a low stroke risk, one point was regarded as an intermediate risk, and two or more points were regarded as high stroke risk.

The HAS-BLED bleeding risk score[37] was defined as one point each for hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, age > 65 years, medication predisposing to bleeding, and alcohol-related disease, not accounting for labile PT-INR which was not available. Low bleeding risk was estimated at zero to one point, intermediate at two points, high at three to five points, and very high bleeding risk at more than five points.

Diagnosis code position

Based on a validation of diagnosis codes for bleedings in the Swedish Patient register,[151] any diagnosis code position was accepted for bleeding outcome events. For thromboembolic events, including ischaemic stroke, only primary and secondary diagnosis codes were considered.

4.3.2 Study I

Study I is a retrospective cohort study of outcome events that compares those with and without OAC treatment and analyses cancer and non-cancer patients separately. All individuals with an AF diagnosis in the Patient Register were included at the first registered AF diagnosis between 1 July 2005 and 1 October 2017, defining index. Baseline was defined as 90 days after index. This blanking period was applied in order not to miss out on OAC initiation after AF diagnosis as well as to avoid overestimation of event rates due to possible double-counting of diagnosis codes at clinic transfer after stroke. Comorbidity data was collected until baseline. Exposure was OAC use, defined as dispensation of OAC from four months before and up to baseline. The reference was not having dispensed OACs.

4.3.3 Study II

All patients discharged alive after the first registered ischaemic stroke event between 1 July 2005 and 30 December 2017 in Riksstroke, and an AF diagnosis according to the Patient Register at the latest at discharge, were included.

The first part of Study II was a cross-sectional study of OAC prescription at the time of discharge. The second part of Study II was a retrospective cohort study of OAC dispensation during follow-up. The date of discharge was defined as baseline. The exposures were cancer and discharge after the introduction of NOACS whereas the corresponding references were non-cancer and discharge before the introduction of NOACs.

4.3.4 Study III

Study III is a retrospective cohort study comparing outcome events in OAC treated AF patients with and without cancer. All those with an AF diagnosis between 1 January 2006 and 31 December 2017, having dispensed at least one OAC prescription at the earliest six months before the AF diagnosis and at the latest 30 December 2017, were included. The first registered OAC dispensation was defined as baseline. Exposure was cancer while the reference was no cancer.

4.4 OUTCOMES AND FOLLOW-UP

Table 4: Outcome definitions

Variables	ICD-10/procedure/ATC code beginning with
Ischaemic stroke	I63
Extracranial arterial thromboembolism	I74
Intracranial bleeding	I60, I61, I62, S064, S065, S066
Gastrointestinal bleeding	I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K661, K920, K921, K922
Bleedings (hospital treated major or non-major clinically relevant bleedings)	D629, I312, M250, R040, R041, R042, R048, R049, R58, H313, H356, H431, R31, N421, N938, N939, KCV22, DR029, and codes for intracranial and gastrointestinal bleedings
OAC	B01AA01 (dicoumarol), B01AA03 (warfarin), B01AF01 (rivaroxaban), B01AF02 (apixaban), B01AF03 (edoxaban), B01AE07 (dabigatran)

4.4.1 Study I

The primary outcome was cerebrovascular benefit defined as reduced risk of the combined endpoint ischaemic stroke/intracranial bleeding. The secondary outcomes were the composite adverse events (consisting of ischaemic stroke, extracranial arterial thromboembolism, bleedings, and death) as well as bleedings and death as separate endpoints. Follow-up was initiated at baseline and ended by the outcome event of interest registered in the Patient Register, emigration, death as stated by the Cause of Death Register, or end of follow-up (31 December 2017).

4.4.2 Study II

The primary outcome for the cross-sectional/descriptive part of the study was OAC prescription at discharge after ischaemic stroke. For the cohort part of the study the primary outcome was OAC dispensation after discharge, whereby follow-up started at discharge, and ended by what came first of the outcome event, emigration, death, one year since discharge, or study end (31 December 2017).

4.4.3 Study III

The primary outcome was cerebrovascular benefit defined as reduced risk of ischaemic stroke or intracranial bleeding. The secondary outcome was bleedings, defined as an admission to a hospital with a bleeding diagnosis. Follow-up was initiated by the first OAC dispensation adjacent to first AF diagnosis, and ended by either the outcome event, emigration, death, or end of follow-up (31 December 2017), whichever came first.

4.5 STATISTICAL METHODS

4.5.1 General

Descriptive data were presented as means or proportions. Differences between groups were described with standardised differences. Incidence rates were presented as events per 100 patient-years. Tests were two-sided and used 95% confidence intervals (CIs). *P*-values < 0.05 and standardised differences > 10% were considered significant.

All analyses were performed using Stata version 15.1 (StataCorp, College Station, TX, USA).

4.5.2 Study I

Analyses were made in cancer and non-cancer patients, separately.

A propensity score for the likelihood of OAC use at baseline was obtained by logistic regression including age, sex, heart failure, hypertension, diabetes, prior ischaemic stroke, prior transient ischaemic attack (TIA), vascular disease, prior bleeding, anaemia, recent venous thromboembolism, chronic obstructive pulmonary disease (COPD), dementia, alcohol-related disease, obesity, thyroid disease, liver disease, prior percutaneous coronary intervention (PCI), cardioversion, two or more falls causing hospital visits, time since first registered AF diagnosis, and amongst cancer patients the presence of metastases. We made a greedy nearest neighbour propensity score matching 1:1 without replacement, using a calliper width of 0.001. Multiple imputation was conducted for missing data regarding the metastasis variable.

Hazard ratios (HRs) with 95% CIs were calculated for the studied outcomes using the Cox proportional hazards model on propensity score matched data. Fine and Gray's proportional subhazards model was used to take the competing risk of death owing to other causes than the studied outcome event into account. This semiparametric model focuses on the cumulative incidences function, indicating the likelihood of the outcome event to occur before a certain time.

Main analyses were conducted for the entire follow-up time. Sensitivity analyses were performed for a maximum follow-up time of one year, and restricted analyses were made on patients without a diagnosis of venous thromboembolism for six months before baseline. Analyses were also performed on warfarin vs. NOAC treated patients. To assess possible residual confounding after propensity score matching, analyses for a falsification composite endpoint comprising cholecystitis, acute bronchitis, herpes zoster infection, cholelithiasis, ankle distortion, and lumbago, which do not have a known relation to OAC use, was made.

4.5.3 Study II

Associations between OAC prescription at discharge and age, sex, and non-overlapping covariates with a significance level of 10% in the univariate analyses were analysed with logistic regression and were presented as odds ratios (ORs). A recent AF diagnosis was defined by a first diagnosis within maximum one month before baseline. The year of discharge was used as an ordinal variable for the time periods 2005–2008, 2009–2011, 2012–2014, and 2015–2017, which facilitated analyses comparing time periods before and after the introduction of NOACs. We categorised hospitals as community, specialised non-university, or university.

The Kaplan-Meier method was used for calculating cumulative incidence of OAC dispensation and a Cox proportional hazards model was used for calculating HRs for first drug dispensation during the year following discharge.

Adjustment for possible clustering of treatment decisions within the same hospital was made using generalised estimating equations with an exchangeable correlation structure for logistic regressions and a shared frailty model with gamma distribution using hospital as a random effect for the Cox regressions. For the analyses adjusting for death as a competing risk during follow-up, we applied the Aalen-Johansen non-parametric method for the cumulative dispensation and the Fine and Gray's proportional subhazards model for the adjusted analyses.

4.5.4 Study III

We included heart failure, hypertension, age, diabetes, prior ischaemic stroke/TIA/extracranial arterial emboli, vascular disease, sex, year of OAC initation, and NOAC (instead of warfarin) use in all multivariable Cox proportional hazards models. For the analyses of the endpoint all bleedings we also included: anaemia, prior major bleeding, impaired kidney function, liver disease, alcohol-related disease, and frequent falls. For the analyses of the endpoint gastrointestinal bleedings the following were added: anaemia, prior major bleeding, liver disease, and alcohol-related disease. Prior intracerebral bleeding, impaired kidney function and frequent falls were added for the analyses of the endpoint intracranial bleedings.

All analyses were adjusted for the competing risk of death due to other causes than the studied endpoint. We used the Aalen-Johansen non-parametric method to estimate the cumulative incidences of the outcome events, and the Fine and Gray's proportional subhazards model for the adjusted analyses.

4.6 ETHICAL CONSIDERATIONS

The studies of this thesis conform to the Declaration of Helsinki, being approved by the regional ethics committee (EPN 2018/1252-31). Consistent with the approval, individual patient consent was not required or obtained. According to regulations protecting the integrity of the patients, an opt-out model for patient consent was used by the Riksstroke register. The risk of violating individual patients' integrity within the context of these large sets of anonymised data generating aggregated results was very low.

5 RESULTS

5.1 STUDY I: Net benefit of OAC treatment in AF patients with and without cancer

Patient characteristics at baseline

After propensity score matching on OAC treatment, patients with cancer consisted of two groups with 7,236 in each, with and without OAC treatment at baseline. Amongst non-cancer patients the corresponding matching procedure resulted in the two groups of non-cancer patients with 152,143 patients each, with and without OAC treatment at baseline (Figure 10).

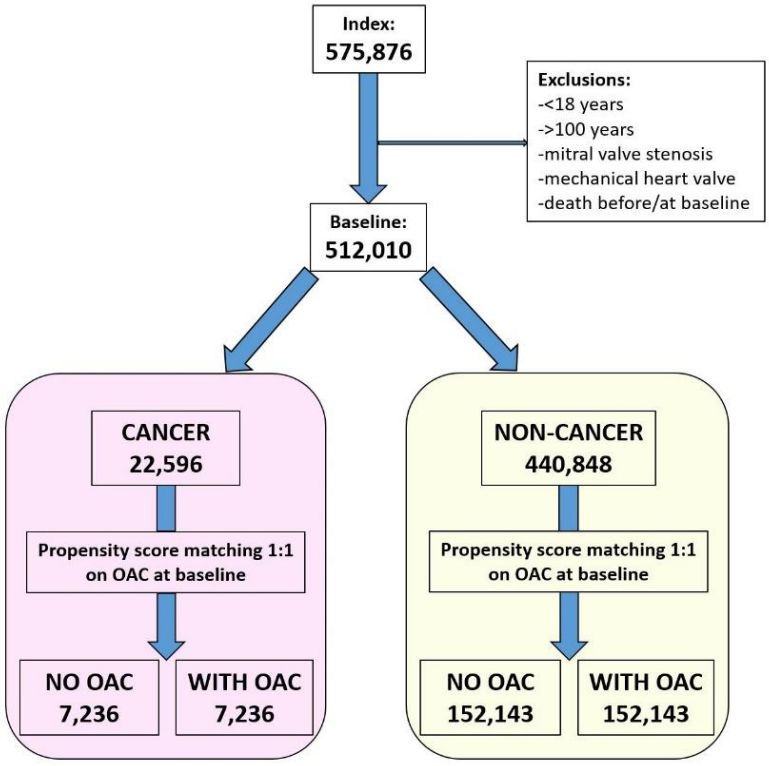

Figure 10: Selection and number of patients. Index defined as first AF diagnosis during the period 1 July 2005 to 1 October 2017. Baseline defined as index + blanking period of 90 days. Illustration reproduced with permission from the publisher.

Co-factors were well balanced between patients with and without OAC treatment at baseline in both cancer and non-cancer patients. Patients were followed for a mean of 2.4 years (interquartile range 0.8–5.4 years).

Primary outcome

Cerebrovascular events

Accounting for the competing risk of death, OAC treatment was associated with a risk reduction of 20% (subhazard ratio [sHR]: 0.80, CI: 0.78–0.81) over the entire study period in non-cancer patients. Amongst cancer patients, a significant association with a decrease in cerebrovascular events was seen when follow-up time was limited to maximum one year (sHR: 0.67, CI: 0.55–0.83). This applied to ischaemic stroke (sHR: 0.54, CI: 0.43–0.69) as well. Analyses within each cancer type subgroup showed no significant associations between OAC treatment and cerebrovascular events.

Secondary outcomes

Adverse events (composite of ischaemic stroke, extracranial arterial thromboembolism, bleedings, and death)

OAC treatment was associated with lower risk of adverse events compared to no OAC treatment in both cancer patients (HR: 0.81, CI: 0.78–0.85) and non-cancer patients (HR: 0.81, CI: 0.80–0.82).

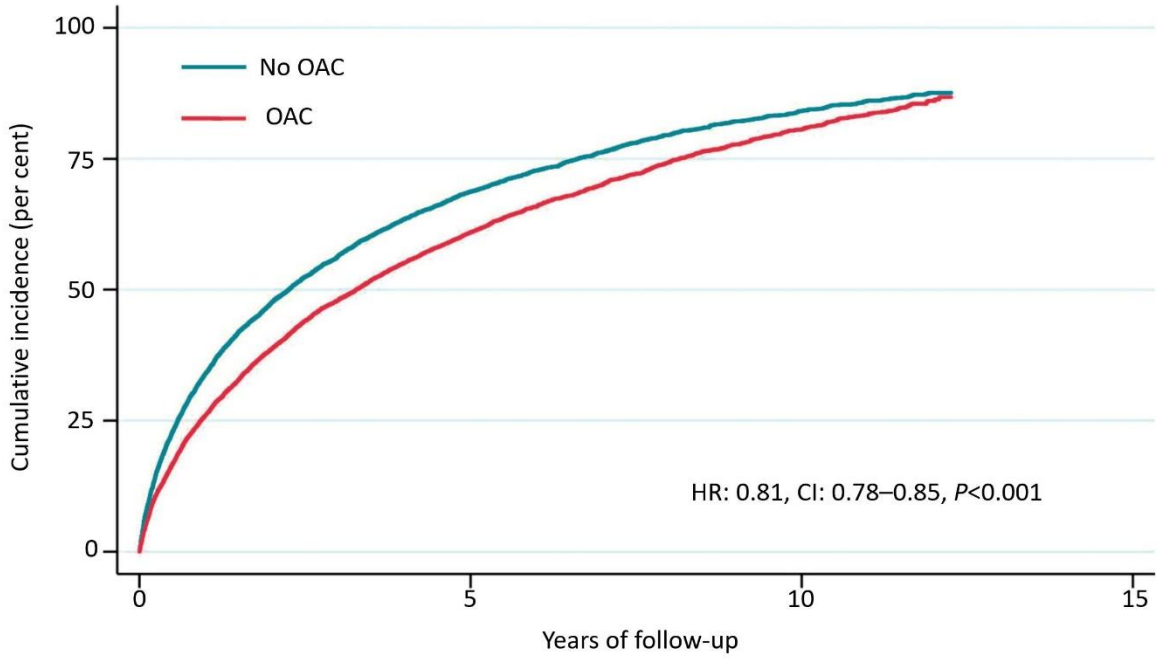

Figure 11: Cumulative incidence of adverse events in relation to OAC treatment amongst AF patients with cancer. Patients propensity score matched on OAC treatment at baseline. Graph reproduced with permission from the publisher.

When analyses were performed for patients of various stroke risk levels, benefit from OAC treatment was seen for cancer patients with intermediate and high stroke risk (Table 5).

Table 5: Adverse events: Analyses for different stroke risk levels in AF patients with vs. without OAC treatment. Cancer and non-cancer patients separately propensity-score matched on OAC use at baseline. Significant *P*-values in italics.

		CANCER			NON-CANCER		
		Adverse events			Adverse events		
CHA_2DS_2-VASc stroke risk level		**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
any	no OAC	reference			reference		
	with OAC	0.81	0.78–0.85	**<0.001**	0.81	0.80–0.82	**<0.001**
low	no OAC	reference			reference		
	with OAC	1.25	0.82–1.91	0.307	1.13	1.05–1.21	**0.001**
intermediate	no OAC	reference			reference		
	with OAC	0.82	0.70–0.96	**0.014**	1.00	0.96–1.04	0.911
high	no OAC	reference			reference		
	with OAC	0.82	0.79–0.86	**<0.001**	0.79	0.78–0.80	**<0.001**

Analyses within each cancer type subgroup showed that OAC treatment was associated with lower risk of adverse events for all cancer types, except for pancreatic, lung and prostate cancer, where no differences were seen. Excluding cancer patients with previous venous thromboembolism did not alter the association between OAC treatment and lower risk of adverse events (HR: 0.82, CI: 0.79–0.86).

Bleedings

After adjusting for the competing risk of death, OAC treatment was associated with higher risk for hospital-treated bleedings amongst cancer patients (sHR: 1.09, CI: 1.02–1.17). However, when limiting follow-up time to maximum one year, there was no such significant association (sHR: 0.93, CI: 0.84–1.03), including intracranial bleedings (sHR: 1.03, CI: 0.72–1.46). Analyses within each cancer type subgroup showed that OAC was associated with a significantly higher bleeding risk only amongst patients with urological cancer.

Death

OAC treatment was associated with lower mortality amongst cancer patients (HR: 0.79, CI: 0.76–0.82), mostly depending on clear associations seen in those with intermediate (HR: 0.77, CI: 0.64–0-93) and high (HR: 0.79, CI: 0.75–0.82) stroke risks. The lower mortality remained after limiting follow-up time to maximum one year (HR: 0.68, CI: 0.64–0.73).

Warfarin vs NOACs

In OAC treated cancer patients, NOACs were associated with lower risk for cerebrovascular events than warfarin (sHR: 0.65, CI: 0.48–0.88). This was driven by the decrease in ischaemic stroke events (sHR: 0.45, CI: 0.30–0.69).

5.2 STUDY II: Secondary prevention with OACs after ischaemic stroke amongst AF patients with and without cancer, before and after the introduction of NOACs

Patient characteristics

At stroke onset and discharge

From Riksstroke 52,471 patients (53.1% women) who had suffered an ischaemic stroke fulfilled the inclusion criteria. Amongst these, 1,518 had cancer and 50,953 had no cancer. Urological cancer (31.0%) and gastrointestinal cancer (27.7%) were the most common cancer types. At stroke onset 21.4% of the included patients used OACs. Cancer and non-cancer patients were alike regarding OAC use, inclusion year, need of home assistance, stroke severity, and hospital type. The majority of patients (46.9%) were treated at specialised non-university hospitals.

Cancer and non-cancer patients did not differ significantly regarding CHA_2DS_2-VASc scores (5.9 points). Compared with non-cancer patients, cancer patients had a marginally higher HAS-BLED score of 3.5 points (vs. 3.3 points) and more often had a previously diagnosed AF, venous thromboembolism, COPD, defects of function in platelets or coagulation, and previous gastrointestinal bleedings or anaemia. Cancer patients were less often women or individuals with dementia. There were no differences between cancer and non-cancer patients regarding discharge destination and proportion of prescribed platelet inhibitors at discharge. Differences in stroke and bleeding risks observed between cancer and non-cancer patients remained when comparing the time periods before and after NOAC introduction (Table 6).

Table 6: Comparison of the time periods 2005–2011 and 2012–2017: Stroke and bleeding risk scores in patients with AF and ischaemic stroke, cancer vs. non-cancer patients. Standardised differences > 0.10 in bold.

Risk scores at discharge	**2005–2011**			**2012–2017**		
	Cancer	**Non-cancer**	Standardised difference	**Cancer**	**Non-cancer**	Standardised difference
CHA_2DS_2-VASc score (mean)	5.8	5.8	-0.005	6.0	5.9	-0.093
HAS-BLED score (mean)	3.4	3.2	**-0.231**	3.6	3.4	**-0.175**

Comparing cancer types over time revealed an increase in the proportion of gastrointestinal cancers, but a decrease of urological and breast cancers (Table 7).

Table 7: Comparison of the time periods 2005–2011 and 2012–2017: Cancer characteristics at the time of discharge after ischaemic stroke. Standardised differences > 0.10 in bold.

Cancer patients	**2005–2011** n = 767[a]	**2012–2017** n = 751[b]	Standardised difference
Cancer site			
Breast	10.0%	7.1%	**0.107**
Gastrointestinal	24.5%	30.9%	**0.143**
Gynaecological	5.9%	5.2%	0.029
Haematological	6.4%	8.4%	0.077
Intracranial	0.9%	1.3%	0.040
Lung	6.8%	9.2%	0.090
Urological	34.8%	27.0%	**0.169**
Other	12.9%	12.9%	0.000
Metastases*	14.3%	16.8%	0.067

Note: [a] 2.7% of study population 2005-2011. [b] 3.1% of study population 2012–2017. *Missing data on cancer stage 52.8% and 34.8%, respectively.

Primary outcome

OAC prescription at discharge after ischaemic stroke

Comparing the time periods before and after the introduction of NOACs, there was an increase in OAC prescription at discharge of 40.2% amongst cancer patients and of 69.3% amongst non-cancer patients (Table 8).

Table 8: Proportions of AF patients discharged with OAC prescription after ischaemic stroke: cancer vs. non-cancer. Standardised differences > 0.10 in bold.

Time period	**Cancer**	**Non-cancer**	Standardised difference
2005–2011	32.1%	36.5%	0.094
2012–2017	45.0%	61.8%	**0.342**

As illustrated in Figure 12, the increase in OAC prescriptions at discharge was proportional to the increase in NOACs.

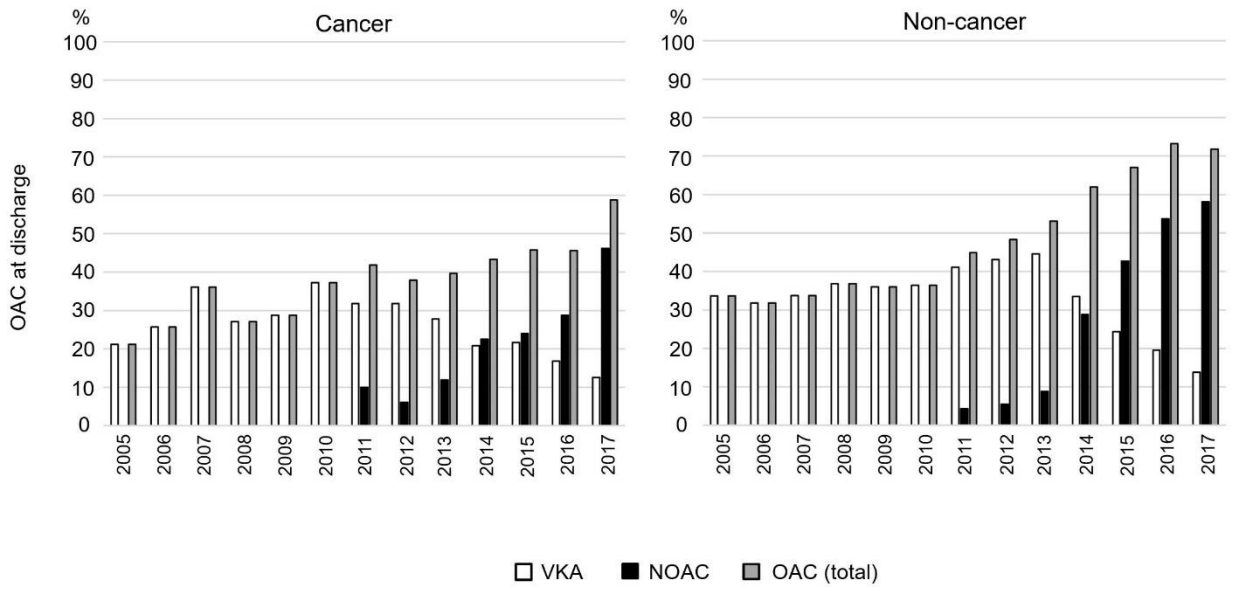

Figure 12: Proportion of AF patients prescribed OACs at discharge after ischaemic stroke 2005–2017.

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Overall, OAC prescriptions at discharge were inversely related to both stroke and bleeding risks in cancer as well as in non-cancer patients. Differences between cancer and non-cancer patients were greater after the introduction of NOACs.

Several predictors of OAC prescription at discharge were observed amongst cancer patients: later year of discharge, OAC use at the time of stroke onset, no previous home assistance, and discharge back to own home. Patients who were older, had dementia, or had had previous ischaemic stroke or major bleedings were less likely to be prescribed OACs at discharge. In relation to individuals with gastrointestinal cancer, those with lung cancer were less likely to be prescribed OACs, and patients with gynaecological and urological cancer had a greater chance of prescription.

Secondary outcomes

Dispensation of OACs after ischaemic stroke: temporal trends

Follow-up time after the introduction of NOACs, compared with before, was associated with higher likelihood of OAC dispensation. However, this was more pronounced in non-cancer patients (HR: 2.02, CI: 1.97–2.07) than in cancer patients (HR: 1.52, CI: 1.30–1.79).

During the time period before the introduction of NOACs, the cumulative OAC dispensation after one year of follow-up did not differ significantly between cancer and non-cancer patients. After NOACs had been introduced, however, cancer patients had dispensed less (estimated cumulative incidence 64.5%) than non-cancer patients (74.9%) (Table 9).

Table 9: Cumulative OAC dispensation during the year following ischaemic stroke in patients with AF per time period, cancer vs. non-cancer. *P*-values < 0.05 in bold

Time period	**Cancer**	**Non-cancer**	Log rank test
2005-2011	43.8% (40.0–47.9%)	46.0% (45.4–46.7%)	0.073
2012-2017	64.5% (60.2–68.8%)	74.9% (74.3–75.5%)	**<0.001**

The median time to dispensation/censoring was longer in cancer patients (94 days, CI: 81–140), than in non-cancer patients (30 days, CI: 28–31) after the introduction of NOACs (Figure 13).

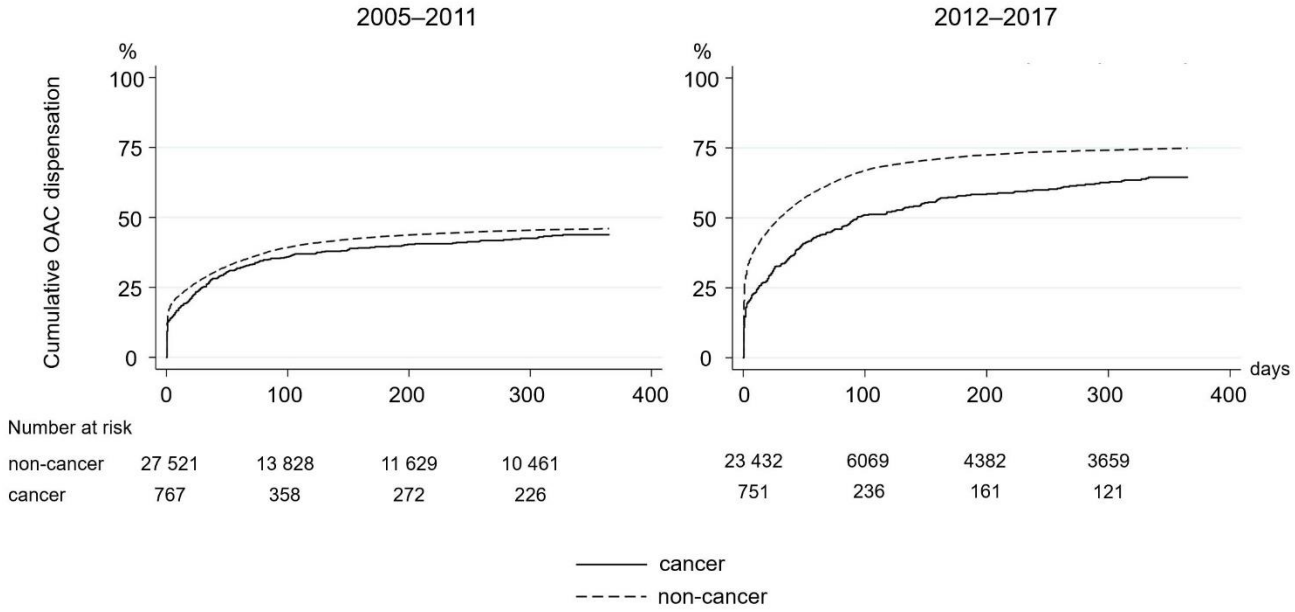

Figure 13: Cumulative OAC dispensation during the year following ischaemic stroke in AF patients per time period, cancer vs. non-cancer. Graphs reproduced with permission from the publisher.

Factors associated with OAC dispensation during follow-up were mostly the same as those seen at discharge, with a few exceptions; cancer patients with a recent AF diagnosis and those with a less severe stroke were more likely to be dispensed OAC (HR: 1.35, CI: 1.13-1.62 and HR: 1.34, CI: 1.00-1.80, respectively). Accounting for the competing risk of death during follow-up, previous major bleedings were negatively associated with OAC dispensation not only in non-cancer patients, but in cancer patients as well (sHR: 0.78, CI: 0.62–0.99).

5.3 STUDY III: Cancer and the benefit-risk relationship in OAC treated AF patients

Patient characteristics

The study population, which is described in Table 10, consisted of patients who were initiated on OAC adjacent to the first registered AF diagnosis during the study time. The proportions of men, patients with more advanced age, history of anaemia, gastrointestinal bleedings, venous thromboembolism, and higher stroke and bleeding risks according to the CHA_2DS_2-VASc and HAS-BLED scores, were higher amongst cancer patients, compared with non-cancer patients. NOAC use did not differ between cancer and non-cancer patients (30.4% vs. 26.8%). Urological cancer was the most common cancer type (35.6%), followed by gastrointestinal cancer (19.1%), haematological cancer (10.7%), breast cancer (9.1%), lung cancer (6.8%), gynaecological cancer (4.9%), and brain tumours (1.3%).

Table 10: Baseline data at OAC initiation: Variables differing significantly between cancer and non-cancer patients. Standardised difference > 10% in bold.

	At OAC initiation		
	Cancer	**Non-cancer**	Standardised difference
N (%)	8,228 (2.5%)	323,394 (97.5%)	
Female	36.5%	43.3%	**0.139**
Age (mean)	75.1	73.1	**-0.211**
Year of OAC initiation			
2005–2011	46.6%	52.8%	**0.123**
2012–2017	53.4%	47.2%	
Risk scores at OAC initiation			
CHA_2DS_2-VASc (mean)	3.0	2.8	**-0.129**
HAS-BLED (mean)	2.3	2.0	**0.188**
Comorbidity at OAC initiation			
Hypertension	55.3%	49.7%	**0.113**
Prior anemia	17.6%	8.0%	**0.290**
Prior gastrointestinal bleed	6.7%	4.2%	**0.108**
Venous thromboembolism < 6 months	9.6%	4.3%	**0.211**

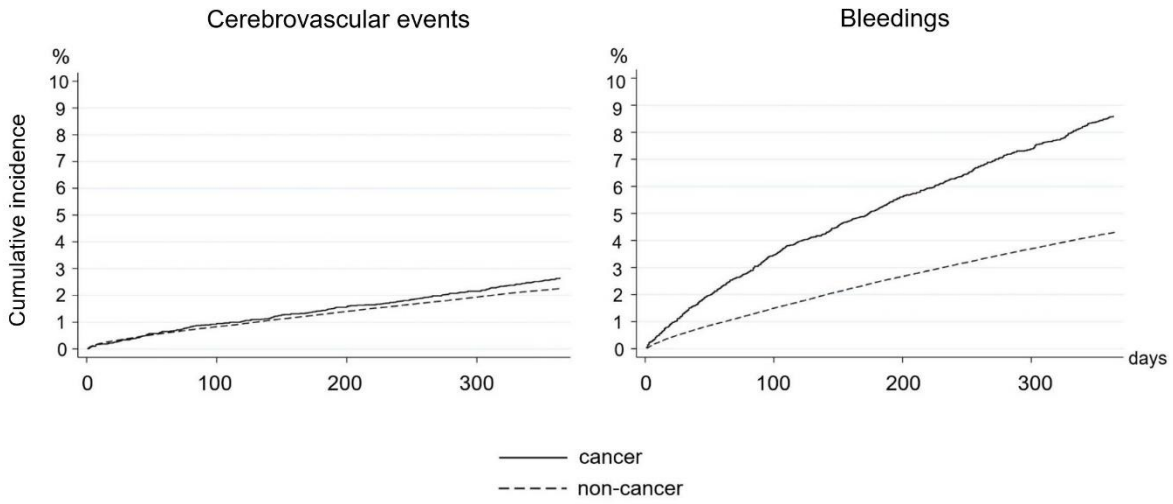

Figure 14: Cumulative incidences of cerebrovascular events and bleedings during the year following OAC initiation in AF patients, cancer vs. non-cancer. Graphs reproduced with permission from the publisher.

Primary outcome

Cerebrovascular events

Accounting for the competing risk of death during follow-up, cancer was generally not associated with higher risk for cerebrovascular events (sHR: 1.12, CI: 0.98–1.29); however, an increased risk was seen for patients with brain tumours (sHR: 3.85, CI: 2.10–7.04) and breast cancer (sHR: 1.52, CI: 1.04–2.22).

Several predictors of cerebrovascular events were identified. Those with the strongest associations were higher age, the thromboembolism composite ischaemic stroke/TIA/extracranial arterial emboli, and prior intracerebral bleeding. NOAC use instead of warfarin use was associated with a lower risk for cerebrovascular events (sHR: 0.78, CI: 0.73–0.83) (Table 11).

Table 11: Adjusted associations with cerebrovascular events accounting for the competing risk of death. sHR=1.00 indicates no significant association. *P*-values < 0.05 in bold.

	Multivariable sHR (95% CI)	***P*-value**
Age ≥ 85 years[a]	2.80 (2.55–3.08)	**<0.001**
Prior ischaemic stroke, TIA or extracranial arterial embolism	2.26 (2.15–2.37)	**<0.001**
Age 75–84 years[a]	2.12 (1.94–2.30)	**<0.001**
Prior intracerebral bleeding	2.11 (1.77–2.52)	**<0.001**
Age 65–74 years[a]	1.44 (1.31–1.57)	**<0.001**
Impaired kidney function	1.20 (1.08–1.34)	**0.001**
Diabetes	1.20 (1.13–1.27)	**<0.001**
Hypertension	1.19 (1.13–1.26)	**<0.001**
Frequent falls	1.14 (1.02–1.26)	**0.016**
Cancer	1.12 (0.98–1.29)	0.097
Vascular disease	1.07 (1.02–1.14)	**0.013**
Year of OAC initiation[b]	1.02 (1.01–1.03)	**<0.001**
Female sex	0.98 (0.93–1.03)	0.387
Heart failure	0.95 (0.89–1.00)	0.057
NOAC treatment[c]	0.78 (0.73–0.83)	**<0.001**

[a]Reference: Age < 65 years; [b]Reference: 2005; [c]Reference: Warfarin treatment.

Secondary outcomes

Bleedings

During the follow-up year after OAC initiation, cancer patients had an overall 69% higher risk for bleedings than non-cancer patients (sHR: 1.69, CI: 1.56–1.82). Of all bleedings, 25.8% were gastrointestinal, and 16.0% were intracranial. The risk for gastrointestinal bleedings was higher amongst those with gastrointestinal (sHR: 1.70, CI: 1.28–2.26), urological (sHR: 1.59, CI: 1.23–2.07), and haematological cancer (sHR: 1.58, CI: 1.04–2.41). Intracranial bleedings were associated with brain tumours (sHR: 8.59, CI: 4.12–17.90), and breast cancer (sHR: 2.35, CI: 1.33–4.16). No statistically significant associations were seen between cancer and fatal bleedings in general (sHR: 1.17, CI: 0.80–1.70) or with fatal intracranial bleedings (sHR: 1.13, CI: 0.71–1.82) taking the competing risk of deaths due to other causes into account.

Besides cancer, some other significant predictors of bleedings were: advanced age, anaemia, impaired kidney function, alcohol-related disease, and prior major bleedings. NOAC instead of warfarin use was associated with lower risk for bleedings (sHR: 0.78, CI: 0.74–0.81). (Table 12) Restricting analyses to NOAC users showed no statistically significant increase for intracranial bleedings in the presence of cancer (sHR: 1.41, CI: 0.93–2.15).

Table 12: Adjusted associations with bleedings events accounting for the competing risk of death. sHR=1.00 indicates no significant association. *P*-values < 0.05 in bold.

	Multivariable sHR (95% CI)	***P*-value**
Age ≥ 85 years[a]	2.80 (2.62–3.01)	**<0.001**
Age 75–84 years[a]	2.26 (2.13–2.41)	**<0.001**
Prior anaemia	1.94 (1.85–2.04)	**<0.001**
Cancer	1.69 (1.56–1.82)	**<0.001**
Impaired kidney function	1.66 (1.56–1.76)	**<0.001**
Age 65–74 years[a]	1.56 (1.46–1.66)	**<0.001**
Alcohol-related disease	1.50 (1.37–1.65)	**<0.001**
Prior major bleeding	1.42 (1.34–1.51)	**<0.001**
Liver disease	1.36 (1.19–1.54)	**<0.001**
Frequent falls	1.26 (1.18–1.35)	**<0.001**
Heart failure	1.24 (1.19–1.29)	**<0.001**
Vascular disease	1.20 (1.16–1.25)	**<0.001**
Hypertension	1.17 (1.13–1.22)	**<0.001**
Diabetes	1.17 (1.13–1.22)	**<0.001**
Prior ischaemic stroke, TIA or extracranial arterial embolism	1.06 (1.02–1.10)	**0.006**
Year of OAC initiation[b]	1.06 (1.05–1.07)	**<0.001**
Female sex	0.91 (0.88–0.94)	**<0.001**
NOAC treatment[c]	0.78 (0.74–0.81)	**<0.001**

[a]Reference: Age < 65 years; [b]Reference: 2005; [c]Reference: Warfarin treatment.

6 METHODOLOGICAL CONSIDERATIONS

6.1 INTERNAL VALIDITY

Two major determinants of internal validity of observational studies are study design and handling of systematic errors.

Study design

Interventional studies are mostly prospective and tailored to evaluate direct impacts of exposure on outcome. Observational studies are often retrospective and used to assess potential causality between exposure and outcome. The main advantages of the register-based cohort designs of our studies are the large amount of nationwide prospectively collected and complete data. Other advantages of a register-based cohort study over a classical drug trial are the possibilities to study prescription and drug use patterns in a real-world setting where follow-up time and endpoints can be flexible. Being an observational study without randomisation, it is only possible to report associations, not causal relationships. Studies I and III are about associations related to efficacy and safety, and Study II is a descriptive cross-sectional study focussing on treatment practices.

Systematic errors

Selection bias

Selection bias arises when the probability of inclusion is influenced by exposure (OAC use, introduction of NOACs, cancer) or outcome (any of the studied outcome events, including prescription and dispensation of OAC). Because Study I is based on all patients in Sweden with an AF diagnosis, this risk is minimised. The main inclusion criterion in Study II was a registered ischaemic stroke in the Riksstroke register, which could be influenced by underreporting, especially amongst patients whose prognosis is too poor to allow for treatment at a hospital or dedicated stroke ward. However, over the time period 2005 to 2017, Riksstroke was estimated to cover about 90% of all patients treated for stroke.[152] In Study III, participation was based on being dispensed OAC, which is to some extent biased toward healthier individuals with better prognosis but is still representative, however, of clinical decisions of a real-world setting.

A limitation of using hospital-associated health care registers is that registered diagnoses are conditioned on hospital contacts, thus giving selection towards heavier comorbidity and possible overestimation of net treatment benefit. Although these nationwide registers offer unique possibilities for epidemiological research, information could be scarce, especially amongst patients who have fewer contacts with the health care system because of social, economic, geographic, or psychiatric reasons. This discrepancy could lead to misclassification of both comorbidity and outcomes and therefore falsely assign some

individuals better health or lower risk. In the case of cancer patients – who are almost exclusively assessed at hospital facilities – we assume that this risk is low. Cancer patients probably have more health care contacts than non-cancer patients, and a higher probability of more registered diagnoses, which could lead to relative overestimating of risks. In Study II, we could take social factors into account to some extent by using information from Riksstroke on, for instance, the need of home assistance.

The strength of all studies is that exposed and unexposed individuals were taken from the same data source.

Information bias/Misclassification

Information bias creates fundamental differences between groups being compared.

Previous validations show that the Swedish National Patient Register, which collects data on all hospital admissions and visits at hospital-associated outpatient units, has positive predictive values for AF of 97%, for stroke of 88%, and for other diagnoses, amongst them bleedings, in the range 85–95%.[153] The Cancer Register includes information on location, diagnostic modalities, and stage. According to a previous validation, its completeness regarding diagnosed malignancies is very high, even though there is some site specific underreporting, for example for leukaemias and lymphomas.[154] In the Swedish Cause of Death Register, only about 0.9% of the deaths are missing an underlying cause of death due to underreporting, making the risk of misclassification low.[146]

Because large nationwide health care registers contain mainly binary data, the risk of misclassification of diagnoses still constitutes a potential problem in some situations. For instance, in line with most other epidemiological research in this field, our studies were built on the assumption that the existence of an AF diagnosis indicates a cardio-embolic origin in the case of an ischaemic stroke. This introduces a possible risk of misclassification of stroke etiology, which might attenuate results. A way of increasing specificity is to use confirming registrations. In Study II, Riksstroke provided information about several diagnoses and drug use, thus backing up information retrieved from the Patient and Drug registers. On the other hand, double-counting of diagnosis codes at clinical transfer could overestimate outcome event rates, which was the reason we applied a blanking period in Study I. The risk of misclassification could be unevenly distributed, for example due to different reporting rates of stage depending on cancer type. To compensate for this, we used multiple imputation of cancer stage in Study I, and subgroup analyses in Study II and III. To avoid underestimating the outcome event of bleeding, we broadened the definition to also include in-hospital blood transfusions.

Information on drug treatment has its own challenges. The chosen approach, beyond the complicated issues of compliance and adherence, was an intention-to-treat-like method, the main limitations of which are overestimation of drug use and attenuation of the drug effect. Warfarin is extra challenging to evaluate because estimation of actual drug effect requires information about PT-INR or TTR, which we did not have. Additionally, warfarin dosage differs greatly between individuals, making approximations of the need for a new prescription

at any chosen time difficult. In order to avoid data on OAC prescriptions leading to overestimation of actual OAC dispensation, we conducted separate analyses for these two entities in Study II. However, a registered dispensation could in its turn overestimate actual drug use, which was not possible to control for in either of the studies. Because we could not distinguish between therapeutic and bridging use of parenteral anticoagulants, these were restricted to sensitivity analyses, which did not change main results (Study I). Cancer treatment was estimated from dispensation of anti-tumoural drugs for self-administration, and procedure codes for in-hospital chemotherapy and radiation. However, cancer treatment is much more differentiated, and the reporting of these kind of procedures has not yet been validated, thus increasing the risk of misclassifying cancer severity.

Confounding bias

A confounder has associations with both exposure and outcome and is not part of the causal link between exposure and outcome. Randomisation – which is often used in drug trials – is an excellent way to distribute confounders evenly between untreated and treated individuals. In these observational studies, however, other methods such as restriction, stratification, cluster analyses, and regression analyses with adjustments were used.

Confounding by indication is the most common limitation of observational treatment studies, and is present in all three studies of this thesis. We used several techniques to minimise this type of bias: by restricting analyses to certain subgroups in sensitivity analyses (Study I, II and III), to those who had recently suffered an ischaemic stroke (Study II), and to patients who had been initiated on OAC treatment (Study III). Additionally, we conducted propensity score matching[155,156] on the likelihood of OAC use at baseline (Study I), adjusted for possible confounders (Study II and III), performed cluster analyses in order to adjust for differences in hospital associated treatment practices (Study II), and stratified on stroke risk (Study I), cancer status (Study I and III), and cancer type (Study I and III). Our analyses showed a nearly doubled mortality in cancer patients. When individuals who are censored do not have the same future risk of an event of interest due to a competing risk such as death, competing risk analysis methods are available. These were used throughout all studies.

The dynamic properties of follow-up time could also increase the risk of confounding bias. A limitation of Study I is the change of treatment practices following revised guideline recommendations regarding both stroke prevention and cancer care during follow-up time. In Study II, which studied the introduction of NOACs, we therefore used time as an exposure variable. In Study III, analyses were adjusted for year of OAC initiation. The potential problem of treatment cross-over during follow-up and the assumed variety in development of cancer disease was reduced by limiting the follow-up time in the subanalyses of Study I and the main analyses of Studies II and III.

Residual or hidden confounding is the systematic difference between exposed and unexposed patients remaining, despite the use of various statistical methods. This can occur in the presence of medical conditions that are difficult to characterise, registered as binary variables even though they are continuous, or that should ideally be measured more than once, for example comorbidity at baseline. One way to check for possible residual confounding after

propensity score matching is the use of falsification endpoints (Study I). The lack of association between OAC treatment and the falsification endpoint suggests that hidden confounding did not affect the results to any great extent.

6.2 EXTERNAL VALIDITY

The studies of this thesis are based on health care registers of prospectively recorded data covering the entire public hospital-associated health care system in Sweden. This is beneficial for the external validity, often referred to as generalisability, not only amongst hospital treated patients in Sweden, but probably also for other countries with similar patient compositions and health care systems. What could influence the generalisability negatively is that private health care and primary health care was not covered by the registers, even though the number of cancer patients missed is assumed to be negligible. Another strength is that the use of health registers includes patients who would most likely be ineligible for clinical trials. Amongst these are elderly patients with heavier comorbidity and perhaps varying attitudes towards treatment and participation in drug trials.

Restricting cancer patients to those with a new diagnosis within one year before baseline was an attempt to somewhat standardise the situation in which clinical decisions on OAC treatment are often made. This increases the generalisability regarding patients with a newly diagnosed and therefore active cancer. However, generalisability regarding patients with a longer history of cancer, including both relapses and remissions, must be cautiously interpreted.

6.3 RANDOM ERROR AND PRECISION

The presence of random errors influence study precision. It is evaluated by the significance level of the statistical analyses that are conducted; this was set to 5% in conformity with most medical studies.

Precision of cohort studies can suffer from small sample sizes and few outcome events. Despite having data covering practically all existing AF patients in Sweden back to 2005, stratifying the cancer group into cancer subtypes generated even smaller groups, thus increasing the risk for type II errors and therefore the risk of not being able to detect possible differences related to OAC treatment. Because the studies were based on the whole existing population, there was no possibility to further expand the data. Interestingly, we found examples that revealed subgroup size did not seem to always matter when finding statistically significant differences. For instance, the increased risk of intracranial bleedings amongst the smallest subgroup of AF patients (brain tumours) (Study III).

7 DISCUSSION

7.1 WHY STUDY OACs IN AF PATIENTS WITH CANCER?

As the ageing population grows, the incidences of both AF and cancer will increase. This highlights the importance of studying the overlap between these two common medical conditions. Several previous studies – which could be criticised for methodological heterogeneity – have not been able to show a generally increased stroke risk amongst AF patients with cancer versus those without cancer, implicating that AF seems to be the clinically most important stroke risk factor regardless of cancer status.[116-119]

OAC treatment of AF patients with concomitant cancer means balancing several kinds of risk. Not only do cancer patients have an increased risk of venous thromboembolism and a higher risk of stroke but also an increased risk of bleeding, including severe bleedings. Until now, no randomised controlled drug trials have been conducted focussing on OAC treatment in AF patients with cancer. This is reflected by the absence of evidence-based guidelines available. Instead, consensus-based recommendations have been published, revealing the need for further research. Although observational studies show associations and not causality, they are valuable sources of information for clinical decision making which is the scope of this thesis. To our knowledge no practice study on secondary stroke prevention amongst AF patients with cancer has been conducted before.

7.2 WHO GETS TREATMENT?

By looking at the descriptive parts of Studies I and II, it is possible to investigate several aspects of who gets OAC treatment and who does not. We found that OAC use amongst AF patients was generally low. Over the entire study period, less than half of the AF patients – among which the majority at elevated stroke risk – were treated. The proportion was even lower amongst patients with cancer (Study I). In patients at the very highest stroke risk (after having suffered an ischaemic stroke), cancer patients were less likely to be treated with OAC despite known AF and a cardiovascular risk profile similar to that of patients without cancer (Study II). This corresponds to previous studies showing lower OAC use in AF patients with increased stroke risk, particularly in the presence of cancer.[21,68]

Factors influencing treatment

Several factors reflecting both frailty at stroke onset and worse stroke outcome were negatively associated with OAC treatment after ischaemic stroke. This was seen also for lung cancer, possibly explained by an often aggressive nature. Overestimation of the excess bleeding risk may be one of the most important reasons why AF patients with cancer are less often treated with OACs. Other factors such as short life expectancy or multifactorial contraindication – for which there are no specific diagnosis codes – could, however, certainly play a role, even though the use of falsification endpoints in Study I suggests low residual

confounding. Another explanation could be the overlap between stroke and bleeding risk factors. However, differences in OAC at discharge between cancer and non-cancer patients generally decreased as bleeding risk increased (Study II). The use of platelet inhibitors instead of OACs for patients at intermediate stroke risk – part of the European AF guidelines until 2010 – could also contribute, especially amongst elderly patients.

Delayed treatment

We found that the proportion of AF patients that dispensed OACs during the year following an ischaemic stroke was higher than the proportion discharged with an OAC prescription. Rates of dispensation were, however, higher in patients without cancer, indicating postponement of the treatment decision in cancer patients. This is further illustrated by the observation that a recently diagnosed AF amongst cancer patients showed no significant association with OAC prescriptions at discharge after ischaemic stroke but was positively associated with dispensation during follow-up. The delayed implementation of secondary stroke prevention with OACs could depend on uncertainty regarding prognosis and further diagnostic or therapeutic procedures during earlier phases of cancer.

The introduction of NOACs

Previous studies of general AF populations have shown that OAC use has increased substantially since NOACs were introduced.[157-159] In Study II, we found that the introduction of NOACs was associated with increased OAC treatment amongst AF patients with cancer, driven by the share of NOACs. The increase was seen both at discharge and during follow-up after ischaemic stroke. Rates of dispensation were, however, higher in non-cancer patients and the difference was even greater after NOACs were introduced. This increase in OACs amongst potentially frail patients is consistent with other large register-based studies from Denmark and Norway that have shown increased OAC treatment in elderly patients since NOACs were introduced.[160,161] Although the introduction of NOACs coincided with major updates of AF guidelines lowering the threshold of treatment, the proportion of cancer patients discharged with any OAC increased by 40.2%, compared to 69.3% in non-cancer patients, despite no change in the differences in stroke and bleeding risk between cancer and non-cancer patients over the study time. Thus, cancer patients did not seem to benefit from the faster treatment decisions that non-cancer patients benefitted from as a result of NOACs. This is problematic considering that AF is an established predictor of early stroke recurrence[162] and that early NOAC initiation post-stroke has a net benefit in the general AF population.[163]

Our interpretation is that the lack of evidence-based guidelines regarding AF patients with cancer challenges and therefore undermines clinical decision making.

7.3 THE CONCEPT OF NET BENEFIT OR HOW TO BALANCE EFFICACY AND HARM

An informed medical decision regarding treatment implies weighing potential benefits versus potential harms. However, there is no consensus on how to incorporate these in a single summary statistic. We chose to use a composite of negative events regardless of thromboembolism or bleedings, thus combining estimations of efficacy and safety. This approach may be criticised due to the difficulty of estimating to what extent a major bleeding endpoint causes more suffering than a thromboembolic event, or the other way around. Previous studies have used different ways to compare the severity of different types of outcomes of a treatment, for example by applying weights depending on how strong the association is between the outcome and death,[48,164] or by arbitrarily giving a 1.5 times higher weight for intracranial bleeding events than for thromboembolic events.[43,165,166] From a clinical point of view, however, it is difficult to categorically imply that bleedings would always override thromboembolic events, especially as register data are often binary. This is a reason why adding quality-adjusted life years to the endpoint has been proposed.[167] Other studies have used multiple models, including the skipping of weights in order to avoid the risk of biasing,[168,169] The complexity of this matter, including the lack of assigning weights and values to benefits and risks has also been highlighted in structured comparisons and evaluations of how the European Medicines Agency and the US Food and Drug Administration communicate benefit-risk decisions regarding new treatments.[170]

In summary, there is no standard procedure to merge benefit and potential harm of treatment in scientific studies, which highlights the possibly even more complex situation faced by clinicians world-wide. Our choice to equate all hospital treated thromboembolic and bleeding events, minimises risks of arbitrary biasing. The risk of underestimating the impact of bleeding is probably compensated by our relatively broad definition of bleedings.

7.4 OACs AND NET BENEFIT

7.4.1 Cancer

In Study III, the possible impact of OAC treatment in regard to cancer was explored. We found that after adjustment for comorbidity and for the competing risk of death, the net cerebrovascular benefit was similar in patients with and without cancer. In addition, cancer contributed to an overall increased risk of bleedings. These findings are in consonance with the post-hoc analyses of the ENGAGE AF-TIMI 48 trial on OAC treated patients with AF in which cancer was not associated with all-cause stroke, but with major bleedings.[171] A post-hoc analysis of the ROCKET AF trial showed similar results, but the bleeding risk of cancer patients was not significant for the specific endpoints ‘increased bleedings in critical organs’, and ‘bleedings requiring blood transfusions’.[172] This differs from our results, but could depend on the relatively low number of outcome events, the exclusion of patients with a life expectancy under two years, and a less precise definition of cancer than we used.

The post-hoc analyses of the ARISTOTLE trial showed no significant associations between cancer and ischaemic stroke or bleedings in OAC treated but comprised 157 patients with

active cancer, challenging the statistical power.[173] Similar conclusions were reported in an observational Danish study but the lack of distinction between previous and present cancer could influence these results.[117] On the other hand, an observational study from Italy on NOAC treated AF patients found elevated risk of both ischaemic stroke and bleedings in the presence of cancer. This study was, however, limited by a rather small cancer group, of which only 104 patients had active cancer.[115]

7.4.2 Cancer type

The issue of possibly different benefit related to cancer types was addressed in the net benefit analyses for different cancer types in both Study I and III. In Study I significant associations were seen mainly in large cancer subgroups, which raises the possibility of type II errors due to low sample sizes. In Study III, however, a significantly stronger association was detected between the smallest group of patients with brain tumours and the higher risk for cerebrovascular events due to higher risk for intracranial bleedings, compared with non-cancer patients. This was also seen for patients with breast cancer, which may be explained in part by increased bleeding risk as a consequence of interaction between warfarin and selective oestrogen receptor modulators used to inhibit tumour growth.[174] Previous studies have shown no increased OAC associated bleeding risk in AF patients with breast cancer compared with AF patients without cancer.[117,175] In contrast to these studies, Study III had a stricter definition of cancer and recorded more events.

Amongst OAC treated AF patients, those with gastrointestinal, urological, and haematological cancers had an increased risk for gastrointestinal bleedings. This is partly in line with previous studies showing a higher risk for gastrointestinal bleedings when treated with anticoagulants, mostly due to local barrier disruptions of the gastrointestinal tract, thrombocytopenia, and invasive procedures or treatments.[124,176,177]

7.4.3 Time since cancer diagnosis

Cancer is a dynamic condition influenced by both diagnostic and therapeutic measures as well as by the cancer itself. Stroke incidence has been seen to be at the highest during the first year after cancer diagnosis.[108,111,178] Therefore, time has the potential to be of importance, especially regarding prognosis. To reduce the possible effect of diverging cancer severity over time in Study I, we additionally limited follow-up time for some analyses, revealing a net cerebrovascular benefit of OAC treatment during the first year following a cancer diagnosis in AF patients.

7.4.4 Stroke risk

There is conflicting data regarding the usefulness of stroke risk scores in cancer patients. For example, it has been suggested that risk scoring works more accurately in patients who already have AF at the time of cancer diagnosis, compared with later AF diagnosis.[90]

According to a previous study, the stroke risk score $CHADS_2$ was found to be more useful than the CHA_2DS_2-VASc score in AF patients with cancer[134] whereas another study has concluded that the CHA_2DS_2-VASc score predicts differently depending on the presence of cancer.[114] Our findings among AF patients with cancer in Study I, however, matched clinically reasonable expectations by suggesting net benefit of OAC treatment for the composite adverse events at elevated stroke risk according to CHA_2DS_2-VASc.

7.4.5 Warfarin vs. NOACs

The question of which kind of OAC to consider in cancer patients – in whom treatment effects are hard to predict – is of great interest. Warfarin can be closely monitored with PT-INR whereas the effect of NOACs can be evaluated only indirectly. Nowadays there are reversing agents against all OACs available.

Our analyses propose a lower risk of ischaemic stroke and a net cerebrovascular benefit with NOACs compared to warfarin amongst AF patients with cancer (Study I). Furthermore, AF patients with cancer using NOACs instead of warfarin seem to have a lower risk for bleedings in general and similar risk of intracranial bleeding as non-cancer patients with the same treatment (Study III). This is in accordance with the main findings of a recent study-level meta-analysis of AF patients with cancer, in which at least the same efficacy of thromboembolic stroke prevention and less bleeding complications was shown for NOACs compared with warfarin.[179] This corroborates drug trials in the general AF population.

7.5 HOW SHOULD WE TREAT?

7.5.1 What do current recommendations say?

Current recommendations regarding stroke prevention in AF patients with cancer are based on consensus. The 2018 European Heart Rhythm Association Practical Guide on the use of NOACs in patients with AF recommends clinicians to look at cancer as a factor to regularly evaluate because of its potential to cause changes in kidney or liver function as well as possible drug-drug interactions with chemotherapy.[142] This resembles the way the European AF guidelines suggest the handling of bleeding risk in the setting of OAC treatment; it is emphasised that an increased bleeding risk score should not automatically result in withholding OAC. Instead, manageable bleeding risk factors should be corrected,[1] which is also stated in the guidelines of the International Society on Thrombosis and Haemostasis.[180] Bleeding data based on cancer patients with venous thromboembolism suggest that NOACs should be used with caution when the patient is affected by luminal gastrointestinal cancers or mucosal abnormalities such as esophagitis, gastritis, duodenal ulcers, or colitis.[181]

To date there is no specific guidance about OACs as secondary prevention after ischaemic stroke for AF patients with cancer.

Anti-tumoural treatment

It is estimated that about one third of patients with cancer receive chemotherapy.[182] Tyrosine kinase inhibitors and monoclonal antibodies can cause bleedings due to thrombocytopenia.[183,184] Most chemotherapy substances are not strong inducers or inhibitors of CYP 3A4 or glycoprotein-P, but in such case, apixaban and rivaroxaban should be used with caution.[180] Previous trials on cancer-related venous thromboembolism that tested NOACs against LMWH in patients with a large proportion on chemotherapy have mostly shown non-inferiority regarding incidence of major bleeding. This indicates that NOACs seem to be safe in this particular setting.[135-138]

According to a guidance on chemotherapy and OAC treatment by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, it is recommended to base decisions on the comparison of possible negative effects of abstaining from either OAC treatment or the anti-tumoural treatment, because it could sometimes be preferable to anticoagulate. It is further stated, that it is also of great importance to take the dynamic characteristics of cancer and its treatment into consideration.[180]

7.5.2 Implications: Practical comments regarding treatment

Awaiting randomised controlled trials with specific focus on AF patients with cancer to guide clinical practice, the findings of this thesis could be combined with the suggestions presented in the guidance from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis[180] and from the 2018 European Heart Rhythm Association Practical Guide on the use of NOACs in patients with AF[142], as follows:

-The net benefit of OAC treatment amongst AF patients with cancer and at least intermediate stroke risk should routinely be taken into consideration according to current guidelines for the general AF population, including the identification of possible manageable bleeding risk factors.

-Amongst AF patients who have had an ischaemic stroke and therefore are at highest stroke risk, awareness of the risk for perfunctory delay of OAC treatment is warranted.

-It is reasonable to continue the current OAC if already prescribed and well managed, while NOACs would be the choice when starting OAC treatment and no drug interactions are expected or gastrointestinal bleeding of concern.

-NOACs seem to be a safe alternative to warfarin, but apixaban and rivaroxaban should be used with caution together with anti-tumoural treatments inhibiting or inducing CYP 3A4 or glycoprotein-P.

-Special caution is advised when the patient is affected by luminal gastrointestinal cancer or mucosal pathologies such as oesophagitis, gastritis, duodenal ulcers, or colitis. Prevention of upper gastrointestinal bleedings with proton-pump inhibitors should be considered.

-The dynamic nature of cancer and changes in kidney and liver function should be accounted for, as well as drug interactions, possible need for surgical interventions, prognosis, and patient preferences.

-In addition to clinical assessments, laboratory work-up regarding signs of drug accumulation and bleeding should be performed regularly after OAC initiation. Extra care should be exercised amongst patients with brain tumours and breast cancer.

-There is no scientific evidence for the use of LMWH as stroke prevention in AF patients with cancer, and safety does not seem higher than that for warfarin. In case of problems with oral intake, however, LMWH could be a time limited treatment option.

-Decisions on stroke prevention with OAC in AF patients should be multi-disciplinary, taking cardiovascular and oncological aspects, as well as prognosis and the patient's preferences into consideration. Regular assessments of the general clinical state should be done, anticipating preparedness to discontinue OAC treatment in terminal patients.

7.6 FUTURE PERSPECTIVES

As the population ages, the cancer incidence increases and cancer survival improves, we will see increasing numbers of people living with both cancer and AF. AF patients with cancer are an important group which needs to be further monitored regarding treatment practices through longitudinal studies, as awareness increases and possibly updated guidelines are implemented. Because present knowledge on warfarin versus NOACs amongst cancer patients comes from retrospective studies and post-hoc analyses of drug trials in general AF populations[117,171-173,185,186] (summarised in the previously cited meta-analysis by Cavallari et al.[179]), there is a need for randomised drug trials of well-defined cancer populations regarding type and stage, as well as of different OACs. Additionally, validations of stroke and bleeding risk scores in well-defined cancer cohorts would also be of great utility for further assistance when making clinical decisions. The HEMORR$_2$HAGES score,[38] which was created as a combination of three previous risk scores and the only bleeding risk score containing a malignancy variable,[187] is an example of a clinical tool that may need further validation.

8 CONCLUSIONS

The results support that: 1) AF patients with cancer and elevated stroke risk benefit overall from treatment with OACs, NOACs in particular; 2) there is probably underutilisation of OACs as secondary stroke prevention amongst AF patients with cancer, despite increased OAC use since NOACs were introduced; and 3) cancer generally does not change net cerebrovascular benefit of OACs, NOACs in particular, amongst AF patients, despite the overall increased risk of bleedings.

9 SVENSK SAMMANFATTNING

Bakgrund

Individer med cancer har högre risk för såväl stroke som blödning jämfört med individer utan cancer. Trots att befolkningen blir allt äldre och gruppen patienter som har både förmaksflimmer och cancer blir större, saknas riktlinjer avseende strokeförebyggande behandling för dessa patienter. Syftet med den här avhandlingen var att beskriva strokeförebyggande behandling med perorala antikoagulantia hos förmaksflimmerpatienter med cancer, därtill att uppskatta nettonyttan.

Metod och resultat

Registerdata avseende alla patienter med minst en registrerad förmaksflimmerdiagnos i det svenska patientregistret mellan 1 juli 2005 och 31 december 2017 samkördes med läkemedelsregistret, cancerregistret, dödsorsaksregistret och Riksstroke. Patienter med en ny cancerdiagnos senaste året och patienter utan cancerdiagnos senaste fem åren inkluderades.

Studie I: Vi använde propensity score matchning avseende sannolikheten att behandlas med perorala antikoagulantia efter en förmaksflimmerdiagnos för att studera patienter med och utan antikoagulantiabehandling. Patienter med (n=14 472) och utan cancer (n=304 286) analyserades separat. Bland dem med cancer sågs nettonytta av perorala antikoagulantia avseende det kombinerade utfallet ischemisk stroke, extrakraniell arteriell tromboembolism, blödningar och död (HR: 0,81; CI: 0,78–0,85). Nettonyttan drevs av patienter med intermediär och hög strokerisk. När uppföljningstiden begränsades till ett år och död som konkurrerande utfall togs med i analysen, sågs nettonytta också avseende cerebrovaskulära händelser för behandling med perorala antikoagulantia generellt (sHR: 0,67; CI: 0,55–0,83) liksom för perorala antikoagulantia av icke vitamin K-antagonisttyp specifikt (sHR: 0,65; CI: 0,48–0,88), jämfört med warfarin.

Studie II: I Riksstroke identifierades alla förmaksflimmerpatienter som drabbats av en ischemisk stroke. Bland dem med cancer (n=1518) ökade andelen som skrevs ut med perorala antikoagulantia med 40,2% efter att perorala antikoagulantia av icke vitamin K-antagonisttyp introducerats, jämfört med 69,3% bland dem utan cancer (n=50 953), detta trots att stroke- och blödningsriskerna förblev liknande mellan grupperna över tid. Uttag av perorala antikoagulantia under året som följde på en ischemisk stroke ökade mindre bland dem med cancer (från 43,8% till 64,5%) än bland dem utan cancer (46,0%–74,9%). Mediantiden till uttag var signifikant längre hos dem med cancer (94 jämfört med 30 dagar) efter att perorala antikoagulantia av icke vitamin K-antagonisttyp introducerats.

Studie III: Den cerebrovaskulära nettonyttan skiljde sig inte mellan cancer- (n=8228) och icke-cancerpatienter (n=323 394) under året efter insättning av perorala antikoagulantia i anslutning till förmaksflimmerdiagnos, inberäknat död som konkurrerande risk (sHR: 1,12; CI: 0,98–1,29). Individer med cancer hade högre risk för icke-dödliga blödningar (sHR: 1,69; CI: 1,56–1,82). Perorala antikoagulantia av icke vitamin K-antagonisttyp var associerade med lägre risk för både cerebrovaskulära händelser och blödningar i jämförelse med warfarin.

Bland dem som behandlades med perorala antikoagulantia av icke vitamin K-antagonisttyp var cancer inte associerad till intrakraniell blödning.

Slutsatser

Förmaksflimmerpatienter med cancer har nettonytta av behandling med perorala antikoagulantia enligt allmänna förmaksflimmerriktlinjer, men de bör övervakas noga avseende blödningar. Perorala antikoagulantia av icke vitamin K-antagonisttyp ter sig säkrare än warfarin, men verkar underutnyttjade som sekundär strokeprevention bland patienter med cancer.

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